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SEARCH REQUEST FORM

Scientific and Technical Inf rmation Center

Requester's Full Name: Josephine YOUNG Examiner #: 79813 Date: 10-18-02
Art Unit: 1623 Phone Number 30[8] 605-1201 Serial Number: 09/868,348
Mail Box and Bldg/Room Location: CM1 8E17 Results Format Preferred (circle): PAPER DISK E-MAIL
8819

If more than one search is submitted, please prioritize searches in order of need. mej

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Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: Cyclic Adenosine Diphosphate Ribose Analogues for Modulating T-Cell & Activity

Inventors (please provide full names): POTTER, Barry V.L.; GUSE, Andreas H.; SCHULZE-Koops, Hendrik; BERG, Ingeborg; MAYR, George W.

Earliest Priority Filing Date: 12-18-1998

For Sequence Searches Only *Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.*

Attached: 1) Current Claim Set 2) Bib Sheet [redacted]

Please search:

(1) methods to modulate [redacted] rise in Ca^{+2} entry via cADPR-mediated pathway. 119340-53-3

(2) relationship between an immune disorder and Ca^{+2} [redacted] levels mediated by cADPR in a T cell.

(3) method to treat an immune disorder using the compd of Formula (2) - see claim 5; Formula (3) or (4) - see claim 20.

(4) claim 19

(5) relationship between an immune disorder and a ryanodine receptor/Ca^{+2} channel.

Assigned to: The University of Bath

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Searcher: _____
Searcher Phone #: _____
Searcher Location: _____
Date Searched: _____
Date Completed: 11-4
Searcher Prep & Review Time: 20
Clerical Prep Time: _____
Online Time: 97

Point of Contact:
Alexandra Waclawiw
Technical Info. Specialist
CM1-6A02 Tel: 308-4910

Type of Search

NA Sequence (#) _____
AA Sequence (#) _____
Structure (#) 2
Bibliographic _____
Litigation _____
Fulltext _____
Patent Family _____
Other _____

Vendors and cost where applicable

STN $ 529.00
Dialog _____
Questel/Orbit _____
Dr.Link _____
Lexis/Nexis _____
Sequence Systems _____
WWW/Internet _____
Other (specify) _____

31
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97

PTO-1590 (8-01)

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=> fil wpids
FILE 'WPIDS' ENTERED AT 09:16:25 ON 04 NOV 2002
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FILE LAST UPDATED:          31 OCT 2002      <20021031/UP>
MOST RECENT DERWENT UPDATE:     200270        <200270/DW>
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     FILE 'WPIDS' ENTERED AT 09:11:29 ON 04 NOV 2002
L1            14 S CADPR OR CADP RIBOSE OR CYCLIC ADP RIBOSE OR CYCLIC ADENOSI
L2            27 S RYANODINE (3A) RECEPT?
L3            17 S L2 AND (CA OR CALCIUM OR CA2#)
L4            16 S L3 NOT L1

     FILE 'WPIDS' ENTERED AT 09:16:25 ON 04 NOV 2002

=> d .wp tech l1 1-14;d .wp tech l4 1-16

L1   ANSWER 1 OF 14  WPIDS (C) 2002 THOMSON DERWENT
AN   2002-599752 [64]   WPIDS
DNC  C2002-169572
TI   New tetrahydrofuran derivatives, useful for treating disease associated
     with the inhibition of a ribosyl, cyclases, transferase or hydrolases,
     e.g. hypertension, angina, arrhythmias, multiple sclerosis or diabetes.
DC   B03
IN   SAUVE, A A; SCHRAMM, V L
PA   (SAUV-I) SAUVE A A; (SCHR-I) SCHRAMM V L; (YESH) UNIV YESHIVA EINSTEIN
     COLLEGE
CYC  98
PI   WO 2002059084 A2 20020801 (200264)* EN   48p
        RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ
            NL OA PT SD SE SL SZ TR TZ UG ZM ZW
         W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK
            DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR
            KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PH PL PT RO
            RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW
     US 2002132783 A1 20020919 (200264)
ADT  WO 2002059084 A2 WO 2002-US371 20020104; US 2002132783 A1 Provisional US
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2001-259720P 20010104, US 2002-38760 20020104
PRAI US 2001-259720P 20010104; US 2002-38760 20020104
AB WO 200259084 A UPAB: 20021007
NOVELTY - New tetrahydrofuran derivatives compounds are new.
DETAILED DESCRIPTION - New tetrahydrofuran derivatives compounds of formula (I) are new.
A = N-, O- or S-linked aryl, alkyl or (hetero)cyclic group;
B and E = H, halo, amino or thio; and
D = primary alcohol, H, O-, N-, C- or S-linked to phosphate, phosphoryl, pyrophosphoryl or adenosine monophosphate through a phosphodiester, C-, N- or S-substituted phosphodiester bridge or to adenosine diphosphate through a phosphodiester or C-, N or S-substituted pyrophosphodiester bridge.
An INDEPENDENT CLAIM is also included for a method of treating a disease or condition associated with an ADP-ribosyl transferase, cyclase or hydrolase enzyme, comprising the administration of (I).
ACTIVITY - Antiangial; Antiarrhythmias; Hypertensive; Neuroprotective.
No biological data available.
MECHANISM OF ACTION - ADP-ribosyl transferase enzyme inhibitor; ADP-ribosyl cyclase enzyme inhibitor; ADP-ribosyl hydrolase enzyme inhibitor; Human CD38 inhibitor. beta -D-1'-nicotinamide-2'-deoxyribofuranoside is a competitive inhibitor for CD38 showing Ki value of 1.0 mu M.
USE - (I) is used in pharmaceutical composition for treating a disease or condition associated with an ADP-ribosyl transferase enzyme, ADP-ribosyl cyclase enzyme, ADP-ribosyl hydrolase enzyme (claimed) e.g. disease associated with a defect in the transmembrane flux of calcium ions into or out of cells, particularly vascular smooth muscle cells, cardiac muscle cells and cells of the nervous system such as angina, arrhythmias, atrial fibrillation, hypertension, paroxysmal supraventricular tachycarrdia, acute disseminated encephalomyelitis, acute transverse myelitis, acute viral encephalitis, adrenoleukodystrophy, adrenomyeloneuropathy, AIDS-vascuolar myelopathy, experimental autoimmune encephalomyelitis, experimental autoimmune neuritis, HTLV-associated myelopathy, Leber's hereditary optic atrophy, multiple sclerosis, progressive multifocal leukoencephalopathy, subacute sclerosing panencephalitis and tropical spastic paraparesis or disease associated with insulin release, e.g. diabetes, lymphocyte activation, bone homeostasis or synaptic plasticity.
ADVANTAGE - (I) is a small, mechanism based inhibitor of human CD38 and has potential for regulation of **cADPR** levels. (I) has potential for the regulation of **cyclic ADP-ribose** levels through CD38 and provides new tools for investigating the various pathways in which ADP-ribosyl transferases, cyclases and hydrolases have been implicated.
Dwg.0/9

L1 ANSWER 2 OF 14 WPIDS (C) 2002 THOMSON DERWENT
AN 2002-479641 [51] WPIDS
DNN N2002-378784 DNC C2002-136481
TI Modulating migratory activity of cells expressing CD38 for treating inflammation, ischemia, asthma, autoimmune disease, arthritis, allergy, by contacting the cells with a CD38 inhibitor or activator.
DC B04 D16 P31
IN LUND, F E; PARTIDA-SANCHEZ, S; RANDALL, T D
PA (TRUD-N) TRUDEAU INST INC; (LUND-I) LUND F E; (PART-I) PARTIDA-SANCHEZ S; (RAND-I) RANDALL T D
CYC 97
PI WO 2002032288 A2 20020425 (200251)* EN 105p

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
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AU 2002013318 A 20020429 (200255)
US 2002127646 A1 20020912 (200262)

ADT WO 2002032288 A2 WO 2001-US32383 20011017; AU 2002013318 A AU 2002-13318 20011017; US 2002127646 A1 Provisional US 2000-241065P 20001017, US 2001-982616 20011017

FDT AU 2002013318 A Based on WO 200232288

PRAI US 2000-241065P 20001017; US 2001-982616 20011017

AB WO 200232288 A UPAB: 20020812

NOVELTY - Modulating (M1) the migratory activity of cells expressing CD38, comprising contacting the cells with a CD38 inhibitor or activator, is new

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) an isolated nucleic acid molecule (I) comprising the DNA sequence (S1) of 1073 nucleotides, that encodes SM38 (Schistosoma mansoni CD38 homolog) protein with a sequence (S2) of 303 amino acids fully defined in the specification;

(2) an isolated nucleic acid molecule that is a SM38 antisense molecule;

(3) an isolated polypeptide, termed SM38 (II) comprising S2, or a sequence encoded by a nucleotide sequence that hybridizes to (I) under stringent conditions or moderately stringent conditions and encodes a functionally equivalent gene product;

(4) a purified fragment (III) of SM38 protein comprising the cyclase domain of the SM38 protein;

(5) a chimeric protein comprising (III) consisting of at least 6 amino acids fused by a covalent bond to an amino acid sequence of a second protein, in which the second protein is not a SM38 protein;

(6) an antibody (IV) which is capable of binding a SM38 protein;

(7) a recombinant cell (V) containing a nucleic acid that hybridizes to (I);

(8) identifying (M2) a compound that activates CD38 or SM38 enzyme activity, by:

(a) contacting a cell expressing CD38 or SM38 with a test compound in the presence of a substrate and measuring the level of SM38 or CD38 activity;

(b) in a separate experiment, contacting a cell expressing CD38 or SM38 protein with a vehicle control in the presence of substrate and measuring the level of CD38 or SM38 activity, where the conditions are essentially the same as in (a); and then

(c) comparing the level of CD38 or SM38 activity in (a) and (b), where an increased level of CD38 or SM38 activity in the presence of the test compound indicates that the test compound is a CD38 or SM38 activator;

(9) identifying (M3) a compound that inhibits CD38 or SM38 enzyme activity, by:

(a) contacting a cell expressing CD38 or SM38 with a test compound in the presence of chemoattractant and substrate and measuring the level of SM38 or CD38 activity;

(b) in a separate experiment, contacting a cell expressing CD38 or SM38 protein in the presence of substrate and measuring the level of CD38 or SM38 activity, where the conditions are essentially the same as in (a); and then

(c) comparing the level of CD38 or SM38 activity in (a) and (b), where an decreased level of CD38 or SM38 activity in the presence of the

test compound indicates that the test compound is a CD38 or SM38 activator; and

(10) identifying a compound that modulates the activity of CD38 protein, by contacting a test compound with a CD38 protein, determining whether the compound binds to the CD38 protein, and selecting a test compound that binds to the CD38 protein as a compound that can be used to modulate the activity of the CD38 protein.

ACTIVITY - Antiinflammatory; Vasotropic; Antiasthmatic; Antidiabetic; Antiarthritic; Antiallergic; Immunosuppressive; Antiparasitic.

No biological data is given.

MECHANISM OF ACTION - Modulator of cell migration; Modulator of CD38/SM38 activity.

USE - (V) is useful for producing a CD38 protein. SM38 protein is useful for identifying a compound that modulates the activity of the protein. (M1) is useful for modulating the migratory activity of cells expressing CD38 (claimed) for treating disorders including inflammation, ischemia, asthma, autoimmune disease, diabetes, arthritis, allergies, infection with pathogenic organisms such as parasites, and transplant rejection. (M2) and (M3) are useful for identifying compounds that modulate CD38/SM38 gene expression. The identified compounds are useful in treating disorders associated with migratory activity of CD38-expressing cells such as hematopoietically-derived cells and also pathogenic disorder resulting from infection with pathogenic microorganisms expressing SM38 or structurally related homologous proteins. SM38 is useful in generating antibodies, and identifying other cellular gene products involved in the regulation of SM38 activity.

Dwg.0/19

TECH UPTX: 20020812

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Method: In M2 or M3, the levels of **cADPR**, NAADP (nicotinic acid adenine dinucleotide phosphate), intracellular calcium levels and CD38 mediator cell migration are measured. M2 and M3 further comprise the presence of a chemoattractant in steps (a) and (b) and the cell expressing CD38 expresses a chemoattractant receptor. The CD38 ADP-ribosyl cyclase activity is measured.

Preferred Nucleic Acid: An isolated nucleic acid molecule that hybridizes to (S1) under stringent conditions or moderately stringent conditions and encodes a functionally equivalent gene product or SM38 gene product is also preferred.

L1 ANSWER 3 OF 14 WPIDS (C) 2002 THOMSON DERWENT
AN 2001-611027 [70] WPIDS
DNC C2001-182414
TI Use of nicotinamide and/or a **cyclic adenosine diphosphate-ribose** for the preparation of the medicament for the treatment of hyperproliferative epidermal diseases.
DC B02 B03
IN BLOCH, O; HAREL, A
PA (BLOC-I) BLOCH O; (HARE-I) HAREL A
CYC 94
PI WO 2001051051 A2 20010719 (200170)* EN 38p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2001023929 A 20010724 (200170)
ADT WO 2001051051 A2 WO 2001-IL17 20010109; AU 2001023929 A AU 2001-23929 20010109

FDT AU 2001023929 A Based on WO 200151051
PRAI IL 2000-133976 20000111
AB WO 200151051 A UPAB: 20011129
NOVELTY - A pharmaceutical composition comprises either nicotinamide (NA) and/or **cyclic adenosine diphosphate-ribose** (**cADPR**) or a combination of NA and at least one metabolite of vitamin D3 or vitamin A and a carrier.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following:
(i) inhibiting hyperproliferation of epidermal cells involving contacting the cells with the composition; and
(ii) increasing the anti-oxidative properties of epidermal cells involving contacting the cells with NA (10 mM).
ACTIVITY - Antipsoriatic; Dermatological; Virucide; Antiproliferative.
MECHANISM OF ACTION - Epidermal cell proliferation inhibitor; antioxidant.
HaCat cells (2 x 104/ml) were incubated with NA at a concentration of 5 mN and **cADPR** (25 micro M). The combination of NA and **cADPR** showed a synergistic effect of above 20 % in inhibiting proliferation as compared to the effect of each of these agents alone at the same concentration with respect to Hacat cells. Similarly A 431 (squamous carcinoma cells) (5 x 103 /ml) were incubated with **cADPR** (25 micro M) and NA (2.5 mN). The combination showed a synergistic effect of above 15 % in inhibiting proliferation of the squamous carcinoma cells as compared to the inhibition of each of these components alone.
USE - In the preparation of a medicament for the application and treatment of skin of an individual suffering from benign hyperproliferatine epidermal diseases such as psoriasis, common warts, keratoacanthoma, seborrhoic keratosis, seborrhea and ichthyosis and malignant hyperproliferative epidermal diseases such as squamous-cell carcinoma, basal cell carcinoma and other non-melanoma skin cancers (all claimed) and in cosmetic composition. As anti-cancer and anti-ageing composition.
ADVANTAGE - The composition increases the anti-oxidative properties of epidermal cells to achieve a beneficial effect during treatment. The composition therefore promotes differentiation and inhibits proliferation of human epidermal cells. The long-term NA-treated human keratinocytes are high resistant to hydrogen peroxide-induced oxidative stress, thus indicating that NA serves as a strong antioxidant and therefore a potential anti-aging and anti-cancer protector of human epidermal cells.
Dwg.0/14
TECH UPTX: 20011129
TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Components: The metabolite of the vitamin 3D is 1alpha, 25-dihydroxy-vitamin D3 and the vitamin A metabolite is all-trans retinoic acid.

L1 ANSWER 4 OF 14 WPIDS (C) 2002 THOMSON DERWENT
AN 2001-128255 [14] WPIDS
DNC C2001-038206
TI Detecting onset of diabetes mellitus comprises detecting specific gene mutations in the CD38 gene.
DC B04 D16
PA (BMLB-N) BML KK; (KANE-I) KANETSUKA A; (OKAM-I) OKAMOTO H
CYC 1
PI JP 2000316578 A 20001121 (200114)* 19p
ADT JP 2000316578 A JP 1999-131955 19990512
PRAI JP 1999-131955 19990512
AB JP2000316578 A UPAB: 20010312
NOVELTY - A mutation in the CD38 gene (involved in the production of

cyclic ADP-ribose (cADPR)), is used
to detect the onset of diabetes mellitus.
USE - The method is useful for detecting the onset of diabetes mellitus.
Dwg.0/15

L1 ANSWER 5 OF 14 WPIDS (C) 2002 THOMSON DERWENT
AN 2000-556169 [51] WPIDS
DNC C2000-165398
TI Method for mass production of **cyclic adenosine diphosphate ribose** from nicotinamide adenine dinucleotide - NoAbstract.
DC B02
IN CHANG, S I; HAN, M G; KIM, W H; PARK, H J
PA (ABIA-N) ABI JH
CYC 1
PI KR 99068506 A 19990906 (200051)* 1p
ADT KR 99068506 A KR 1999-19361 19990528
PRAI KR 1999-19361 19990528

L1 ANSWER 6 OF 14 WPIDS (C) 2002 THOMSON DERWENT
AN 2000-442526 [38] WPIDS
DNC C2000-134647
TI Use of compounds capable of antagonizing sustained **cADPR** -mediated rises in intracellular calcium ion levels in T cell in manufacture of medicaments for use in modulating T cell activity.
DC B02 C01
IN BERG, I; GUSE, A H; MAYR, G W; POTTER, B V L; SCHULZE-KOOPS, H
PA (UYBA-N) UNIV BATH
CYC 91
PI WO 2000037089 A1 20000629 (200038)* EN 49p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2000018717 A 20000712 (200048)
EP 1140118 A1 20011010 (200167) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
ADT WO 2000037089 A1 WO 1999-GB4295 19991217; AU 2000018717 A AU 2000-18717 19991217; EP 1140118 A1 EP 1999-962345 19991217, WO 1999-GB4295 19991217
FDT AU 2000018717 A Based on WO 200037089; EP 1140118 A1 Based on WO 200037089
PRAI GB 1998-28071 19981218
AB WO 200037089 A UPAB: 20000811
NOVELTY - Use of a compound capable of antagonizing a sustained **cyclic adenosine diphosphate ribose** (**cADPR**)-mediated rise in intracellular calcium ion (Ca2+) levels in a T cell in response to stimulation of the T cell receptor/CD 3 complex of the T cell in the manufacture of a medicament for use in modulating T cell activity.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:
(1) methods for identifying substances capable of modulating a sustained rise in Ca2+ entry via a **cADPR**-mediated pathway;
(2) compounds (unspecified) identified by these methods; and
(3) process of identifying substances capable of modulating a sustained rise in Ca2+ entry via a **cADPR**-mediated pathway and preparing a quantity of one or more of those substances.
ACTIVITY - Immunomodulatory; antiallergic; antiinflammatory.

The effects of test compounds were examined in the antigen-induced arthritis (AIA) model in female C57BL/6 mice. The mice were immunized at day -21 and -14 with methylated bovine serum albumin (mBSA) in complete Freund's adjuvant. The experimental arthritis was induced at day 0 by injection of mBSA into the right knee joint. Treatment from day 0 (6 hours after injection of mBSA) to day 21 was carried out by daily intraperitoneal injection of 100 micro l of vehicle (0.9% sodium chloride solution; n = 8), 7-deaza-8-bromo-**cADPR** (2a) (0.2 micro mol/kg; n = 5) and, as positive control, Lipotalon (RTM: dexamethasone palmitate) (500 micro g/kg; n = 9). Swelling of the right knee and body weight were determined at days 3, 5, 7, 14 and 21. A reduction in joint swelling was observed at days 3, 5, 7 and 14 was seen with (2a) as compared to vehicle alone. (2a) did not significantly change the body weight during the course of treatment. In marked contrast, Lipotalon (RTM: dexamethasone palmitate) induced a significant reduction in body weight. The results indicate that autoimmune diseases can be successfully treated by **cADPR** antagonists without visible toxic effects.

MECHANISM OF ACTION - **cADPR** antagonist.

Jurkat T cells were preincubated with (2a) and Ca2+ signaling was stimulated by OKT3 and measured by digital ratiometric Ca2+ imaging. On the single cell level, OKT3 stimulated rapid and sustained Ca2+ signaling. Individual cells responded in different ways: oscillation, long-lasting elevations and single spikes, but the majority of cells showed Ca2+ signaling for more than 20 minutes after stimulation. Such long-lasting responses were never observed in the absence of extracellular Ca2+. Pre-incubation with 1 micro M (2a) did not significantly change the pattern of Ca2+ signaling. However, at higher concentrations (10 and 100 micro M), (2a) produced a profound inhibitory effect on the long-lasting Ca2+ entry. In addition, (2a) dose dependently increased the delay between OKT3 addition and the onset of Ca2+ signal indicating that **cADPR** is already involved in the early period of Ca2+ signaling.

USE - The compounds are used to manufacture medicaments for use in modulating the immune response of mammals, to treat autoimmune diseases (thyroiditis, insulitis, multiple sclerosis, iridocyclitis, uveitis, orchitis, hepatitis, Addison's disease, myasthenia gravis, rheumatoid arthritis or lupus erythematosus) or graft rejection, to treat or prevent immune disorders in humans or animals (claimed).

They may also be used to treat disorders including immune hyperreactivity such as allergic reactions, organ-specific autoimmune diseases including insulin-dependent diabetes mellitus, several forms of anemia (aplastic, hemolytic), autoimmune hepatitis, skleritis, myasthenia gravis, idiopathic thrombocytopenia purpura and inflammatory bowel diseases (Crohn's disease, ulcerative colitis) and systemic autoimmune diseases including juvenile arthritis, scleroderma and systemic sclerosis, Sjogren's syndrome, undifferentiated connective tissue syndrome, antiphospholipid syndrome, different forms of vasculitis (polyarteritis nodosa, allergic granulomatosis and angiitis, Wegener's granulomatosis, Kawasaki disease, hypersensitivity vasculitis, Henoch-Schoenlein purpura, Behcet's syndrome, Takayasu arteritis, giant cell arteritis, thrombangiitis obliterans), lupus erythematosus, polymyalgia rheumatica, essential (mixed) cryoglobulinemia, psoriasis vulgaris, psoriatic arthritis, diffuse fasciitis with or without eosinophilia, polymyositis and other idiopathic inflammatory myopathies, relapsing panniculitis, relapsing polychondritis, lymphomatoid granulomatosis, erythema nodosum, ankylosing spondylitis, Reiter's syndrome and different forms of inflammatory dermatitis as well as unwanted immune reactions and inflammation including arthritis, inflammation associated with hypersensitivity, allergic reactions, asthma, systemic lupus erythematosus, collagen diseases and other autoimmune diseases, inflammation associated with atherosclerosis, arteriosclerosis,

atherosclerotic heart disease, reperfusion injury, cardiac arrest, myocardial infarction, vascular inflammatory disorders, respiratory distress syndrome or other cardiopulmonary diseases, inflammation associated with peptic ulcer, ulcerative colitis and other gastrointestinal tract diseases, hepatic fibrosis, liver cirrhosis or other hepatic diseases, thyroiditis or other glandular diseases, glomerulonephritis or other renal and urological diseases, otitis or other oto-rhino-laryngological diseases, dermatitis or other dermal diseases, periodontal diseases or other dental disease, orchitis or epididimo-orchitis, infertility, orchidal trauma or other immune-related testicular diseases, placental dysfunction, placental insufficiency, habitual abortion, eclampsia and other immune and/or inflammatory-related gynecological diseases, posterior, intermediate and anterior uveitis, conjunctivitis, chorioretinitis, uveoretinitis, optic neuritis, intraocular inflammation (retinitis, cystoid macular edema), sympathetic ophthalmia, scleritis, retinitis pigmentosa, immune and inflammatory components of degenerative fondus disease or ocular trauma, ocular inflammation caused by infection, proliferative vitreo-retinopathies, acute ischemic optic neuropathy, excessive scarring (e.g. following glaucoma filtration operation), immune and/or inflammation reaction against ocular implants and other immune and inflammatory related ophthalmic diseases, inflammation associated with diseases or conditions or disorders where, both in the central nervous system (CNS) or in any other organ, immune and/or inflammation suppression would be beneficial.

ADVANTAGE - The compounds have reduced side-effects compared with the prior art.

Dwg.0/4

TECH UPTX: 20000811

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred use - The compound modulates the binding of **cADPR** to a ryanodine receptor/Ca2+ channel. The compound is a **cADPR** analogue. The compound comprises an adenine component to which is individually linked two ribose groups or their derivatives, which are joined via a pyrophosphate bridging group. The compound is of formula (II) or its bio-isosteres or pharmaceutically acceptable salts.

X3 = CR1 or N;
X7 = CR2 or N;
Y = halo, 1-20C hydrocarbyl, N(R3)(R4), OR5, SR6, nitro or carboxyl;
R1-R6 = H or 1-20C hydrocarbyl; and
Z' = H or caging group.

L1 ANSWER 7 OF 14 WPIDS (C) 2002 THOMSON DERWENT
AN 1999-215026 [18] WPIDS
DNC C1999-063359
TI Use of nicotinamide adenine dinucleotide for killing tumor cells or microorganisms - by increasing clonogenic toxicity by imbalancing calcium cytosolic levels or nucleotide pools.
DC B02 C01
IN PERO, R W
PA (OXIG-N) OXI-GENE INC; (PERO-I) PERO R W; (OXIG-N) OXIGENE INC
CYC 81
PI WO 9912951 A1 19990318 (199918)* EN 31p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW
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AU 9894802 A 19990329 (199932)
EP 1015472 A1 20000705 (200035) EN

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JP 2001515916 W 20010925 (200170) 36p
US 6339073 B1 20020115 (200208)
AU 744902 B 20020307 (200229)
MX 2000002455 A1 20010601 (200235)
ADT WO 9912951 A1 WO 1998-US19006 19980909; AU 9894802 A AU 1998-94802 19980909; EP 1015472 A1 EP 1998-948175 19980909, WO 1998-US19006 19980909; JP 2001515916 W WO 1998-US19006 19980909, JP 2000-510756 19980909; US 6339073 B1 Provisional US 1997-58652P 19970911, US 1998-149998 19980909; AU 744902 B AU 1998-94802 19980909; MX 2000002455 A1 MX 2000-2455 20000310
FDT AU 9894802 A Based on WO 9912951; EP 1015472 A1 Based on WO 9912951; JP 2001515916 W Based on WO 9912951; AU 744902 B Previous Publ. AU 9894802, Based on WO 9912951
PRAI US 1997-58652P 19970911; US 1998-149998 19980909
AB WO 9912951 A UPAB: 20000712
NOVELTY - Tumor cells or microorganisms can be killed by contact with nicotinamide adenine dinucleotide (NAD) or its analogs to increase their clonogenic toxicity.
DETAILED DESCRIPTION - An INDEPENDENT CLAIM is included for a kit comprising a compartment containing an amount of NAD or its analogs.
ACTIVITY - Anti-tumor; anti-fungal; anti-parasitic.
MECHANISM OF ACTION - Agonists/antagonists of ADP-cyclase, producing or inhibiting **cyclic ADP ribose** and imbalancing intracellular calcium.
USE - NAD or its analogs are useful for killing tumor cells or microorganisms (claimed). Human promyeloid leukemia line cells exposed to increased doses of nicotinamide adenine dinucleotide (NAD) showed a dose dependent induction of apoptosis, with about 2% apoptosis at NAD dosage of 5000 mu M. The apoptosis was inhibited by the presence of an NADase inhibitor. In tests on mice xenografted with human adenocarcinoma (H2981), a tumor size of 70% compared to a control was seen with a daily NAD dose of 50mg/kg, and no side effects were observed.
Dwg.1/8

L1 ANSWER 8 OF 14 WPIDS (C) 2002 THOMSON DERWENT
AN 1998-609334 [51] WPIDS
CR 1993-143059 [17]; 1995-106153 [14]
DNC C1998-182654
TI Purified **cyclic adenosine di phosphate ribose** - useful for e.g. research, diagnosis and cancer therapy.
DC B04 D16
IN GLICK, D L; HELLMICH, M R; STRUMWASSER, F
PA (GLIC-I) GLICK D L; (HELL-I) HELLMICH M R; (STRU-I) STRUMWASSER F
CYC 1
PI US 5831074 A 19981103 (199851)* 14p
ADT US 5831074 A CIP of US 1988-266145 19881102, CIP of US 1989-404733 19890908, Cont of US 1993-20485 19930222, US 1994-332111 19941031
FDT US 5831074 A Cont of US 5393667
PRAI US 1993-20485 19930222; US 1988-266145 19881102; US 1989-404733 19890908; US 1994-332111 19941031
AB US 5831074 A UPAB: 19981223
Cyclic adenosine diphosphate ribose (**cADPR**) that is at least 85% pure is new.
USE - The **cADPR** can be used as an agent from releasing intracellular calcium ions in therapy and research. It can be labelled and used in assays to identify **cADPR** receptors or can be coupled to a carrier protein and used to produce **cADPR**-specific antibodies for use in immunoassays for research or for diagnosis of diseases

characterised by calcium ion imbalance. **cADPR** can be administered locally to cancer cells to stimulate destruction of the cells by calcium-sensitive proteases.
Dwg.0/5

L1 ANSWER 9 OF 14 WPIDS (C) 2002 THOMSON DERWENT
AN 1998-557090 [47] WPIDS
DNC C1998-166671
TI New **cyclic adenosine** 5'-**di phosphate ribose** analogues - useful in screening for compounds which bind to **cADPR** receptors.
DC B02
IN GALIONE, A; POTTER, B
PA (ISIS-N) ISIS INNOVATION LTD; (UYBA-N) UNIV BATH
CYC 81
PI WO 9843992 A1 19981008 (199847)* EN 30p
RW: AT BE CH DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM GW HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW
AU 9868439 A 19981022 (199910)
ADT WO 9843992 A1 WO 1998-GB921 19980326; AU 9868439 A AU 1998-68439 19980326
FDT AU 9868439 A Based on WO 9843992
PRAI GB 1997-6424 19970327
AB WO 9843992 A UPAB: 19990122
Cyclic adenosine 5'-**diphosphate ribose** (**cADPR**) analogues of formula (I) are new. at least one of X3 and X7 = CR and the other is N; Y = halo, 1-20C hydrocarbon, N(R2), OR, SR, NO2 or COOH; R = H or 1-20C hydrocarbon; Z = H or one Z is a caging group. Also claimed is 7-deaza-8-bromo-**cyclic adenosine** 5'-**diphosphate ribose**.
USE - (I) are used to screen for compounds which bind to **cADPR** receptors by performing a competitive binding assay in which the compounds are caused to compete with (I) for binding to the **cADPR** receptor (claimed). 7-Deaza-8-bromo-**cyclic adenosine** 5'-**diphosphate ribose** is a hydrolysis-resistant antagonist of **cADPR**-induced Ca2+ release. These properties combined with the lipophilic nature of both the CH and Br moieties which render it membrane-permeable, mean that it constitutes a very powerful tool for investigations of **cADPR**-mediated Ca2+ signalling in intact cells.
Dwg.4/4

L1 ANSWER 10 OF 14 WPIDS (C) 2002 THOMSON DERWENT
AN 1997-255546 [23] WPIDS
DNC C1997-082379
TI **Cyclic ADP-ribose** homologues - used as lead compounds for drug development.
DC B02
PA (MATS-I) MATSUDA A
CYC 1
PI JP 09087296 A 19970331 (199723)* 13p
ADT JP 09087296 A JP 1995-272037 19950925
PRAI JP 1995-272037 19950925
AB JP 09087296 A UPAB: 19970606
Cyclic ADP-ribose homologues of formula (Ia) (I; R1, R2 = OH), (Ib) (I; R1, R2 = H) or (Ic) (I; R1+R2 = a bond) and their salts are new: X = N or CH, and Y = NH or O. Also claimed are

nucleoside derivatives of formula (IId) (II; R5, R6 = OR), (IIe) (II; R5, R6 = H) or (IIf) (II; R5+R6 = a bond) and their salts: R = H or protective group for OH, and R3, R4 = OH or optionally protected phosphate residue.
ADVANTAGE - (Ia)-(Ic) are stable equivalents of **cADPR** and are useful as lead compounds for drug development. (IId)-(IIf) are useful as intermediates for the synthesis of (Ia)-(Ic).
Dwg.0/0

L1 ANSWER 11 OF 14 WPIDS (C) 2002 THOMSON DERWENT
AN 1997-191592 [17] WPIDS
DNC C1997-061196
TI New cyclic adenosine tri phosphate ribose, cyclic guanine and hypoxanthine di phosphate ribose - cyclic adenosine tri phosphate ribose stimulates calcium ion release in rat brain microsomes with greater potency than corresp. di phosphate.
DC B02
IN SIH, C J
PA (WISC) WISCONSIN ALUMNI RES FOUND
CYC 1
PI US 5608047 A 19970304 (199717)* 8p
ADT US 5608047 A US 1995-404467 19950315
PRAI US 1995-404467 19950315
AB US 5608047 A UPAB: 19970424
Cyclic adenosine triphosphate ribose (cATPR) of formula (I), cyclic guanine diphosphate ribose (cGDPR) of formula (II:R=H) and cyclic hypoxanthine diphosphate ribose (cHDPR) of formula (II:R = NH2) are new.
USE - No use given, although cATPR stimulates Ca2+ release in rat brain microsomes with greater potency than **cyclic adenosine diphosphate ribose** (**cADPR**).
Dwg.0/2

L1 ANSWER 12 OF 14 WPIDS (C) 2002 THOMSON DERWENT
AN 1996-097112 [10] WPIDS
DNC C1996-031376
TI New **cyclic ADP-ribose** derivs. useful as **cyclic-ADP-ribose** antagonists - with amino, azido, or bromo gp. in 8 position, may contain radio-labels and are useful for treating e.g. hypertension.
DC B02
IN AARHUS, R A; LEE, H; WALSETH, T F
PA (MINU) UNIV MINNESOTA
CYC 1
PI US 5486604 A 19960123 (199610)* 18p
ADT US 5486604 A US 1993-148646 19931101
PRAI US 1993-148646 19931101
AB US 5486604 A UPAB: 19960308
Cyclic ADP-ribose (**cADPR**) derivs. of formula (I) and their acid addn. salts are new. X = NH2, N3 or Br.
USE - (I) are **cADPR** antagonists that block the Ca2+-mobilising activity of **cADPR** and may be used in research for elucidating the mechanism and function of the **cADPR** system. (I; X = N3) could be used as a photoaffinity label for identifying the **cADPR** binding site. **cADPR** antagonists are useful as pharmaceutical agents, e.g. for treating hypertension.
Dwg.0/11

L1 ANSWER 13 OF 14 WPIDS (C) 2002 THOMSON DERWENT
AN 1995-106153 [14] WPIDS
CR 1993-143059 [17]; 1998-609334 [51]

DNC C1995-048369
TI Purified NAD cyclase from gonad of genus Aplysia - useful for prodn. of **cyclic adenosine diphosphate ribose** itself useful for cancer treatment, and for reducing bacterial infection.
DC B04 D16
IN HELLMICH, M R; STRUMWASSER, F
PA (HELL-I) HELLMICH M R; (STRU-I) STRUMWASSER F
CYC 1
PI US 5393667 A 19950228 (199514)* 15p
ADT US 5393667 A CIP of US 1988-266145 19881102, CIP of US 1989-404733 19890908, Div ex US 1990-629101 19901217, US 1993-20485 19930222
FDT US 5393667 A Div ex US 5202426
PRAI US 1990-629101 19901217; US 1988-266145 19881102; US 1989-404733 19890908; US 1993-20485 19930222
AB US 5393667 A UPAB: 19981223
Compsn. enriched for the eukaryotic NAD cyclase (I) of the genus Aplysia, which (I) is enriched by at least 10 fold compared to the NAD cyclase present in a gonad of the genus Aplysia, (I) having an apparent mol. wt. of 24000-34000 daltons after electrophoresis in a sodium dodecyl sulphate polyacrylamide get under a reducing condition is new. Purified (I) which causes prodn. of **cyclic adenosine diphosphate ribose** (**cADPR**) from NAD is claimed per se. (I) is purified from the water sol. fraction of a gonad of the genus Aplysia (embodiment claimed).

USE - (I) is useful for producing purified **cADPR**, the latter being as potent as IP3 in releasing Ca2+ from intracellular stores and thus able to replace IP3 use in the therapy and research. Applicns. of (I) include: causing localised prodn. of **cADPR** (or **cADPR** itself may be locally administered) in cancer cells to cause the specific death of such cancer cells; for routine assays of chemicals and enzymes (eg. assay for NAD); and for use as attractants or affinity agents for bacteria, (I) being useful therapeutically for reducing bacterial infection. E.g. a gene encoding (I) can be inserted into a mammalian cell, such as a macrophage, to cause expression of (I) as an ectoprotein, in order to attract bacteria to the cell which may then engulf the destroy the bacteria.
Dwg.4/5

L1 ANSWER 14 OF 14 WPIDS (C) 2002 THOMSON DERWENT
AN 1993-143059 [17] WPIDS
CR 1995-106153 [14]; 1998-609334 [51]
DNC C1993-064125
TI Purified DNA encoding eukaryotic NAD cyclase - useful for prodn. of **cyclic adenosine di phosphate ribose** from NAD.
DC B04 D16
IN GLICK, D L; HELLMICH, M R; STRUMWASSER, F
PA (MARI-N) MARINE BIOLOGICAL LAB
CYC 1
PI US 5202426 A 19930413 (199317)* 15p
ADT US 5202426 A CIP of US 1988-266145 19881102, CIP of US 1989-404733 19890908, US 1990-629101 19901217
PRAI US 1990-629101 19901217; US 1988-266145 19881102; US 1989-404733 19890908
AB US 5202426 A UPAB: 19981223
Purified DNA (I) of defined sequence is new. (I) is 1191 Gp in length, single-stranded and linear.

USE/ADVANTAGE - (I) ensures a eukaryotic NAD cyclase which causes prodn. of **cyclic adenosine diphosphate ribose** (**cADPR**) from NAD, and pref. also indirectly

inhibits the ADP-ribosyl transferase acitivity of cholera toxin. **cADPR** is as potent as IP3 in releasing Ca2+ from intracellular stores, thus it can be used to replace IP3 in therapy and research. Analogues of **cADPR** can be developed which block the effect of **cADPR** an **cADPR**-receptors aid are thus useful eg. for treating hypertension. Antibodies to **cADPR** may also be used for clinical tests or diagnosis of disease characterised by the presence of Ca2+ imbalance. The NAD cyclase itself may be used to cause localised prodn. of **cADPR** eg. to kill cancer cells, and it may also be used for routine assays of chemicals and enzymes. Finally the NAD cyclase are useful as attractants or affinity agents for bacteria and can be used therapeutically for reducing bacterial infection. (I) enables prodn. of large quantities of the recombinant eukaryotic NAD cyclase.
Dwg.0/5

L4 ANSWER 1 OF 16 WPIDS (C) 2002 THOMSON DERWENT
AN 2002-599269 [64] WPIDS
DNN N2002-475338 DNC C2002-169106
TI Detecting modulators of ion channels for detecting and measuring activity of ion channels, channel-linked receptors or ion transporters expressed in cells, comprises use of a signal-generating thallium sensitive agent.
DC B04 D16 S03
IN WEAVER, C D
PA (BRIM) BRISTOL-MYERS SQUIBB CO
CYC 97
PI WO 2002031508 A1 20020418 (200264)* EN 59p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PH PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2002015350 A 20020422 (200264)
ADT WO 2002031508 A1 WO 2001-US32132 20011012; AU 2002015350 A AU 2002-15350 20011012
FDT AU 2002015350 A Based on WO 200231508
PRAI US 2000-240523P 20001013
AB WO 200231508 A UPAB: 20021007
NOVELTY - Detecting and measuring the activity of ion channels, channel-linked receptors or ion transporters (I) expressed in cells by:
(a) contacting cells expressing (I) with a signal-generating thallium sensitive agent;
(b) contacting the cells with a candidate modulator (III) or (I), and then with assay buffer containing thallium salt solution; and
(c) detecting or measuring the signal generated by (II).
DETAILED DESCRIPTION - Detecting and measuring the activity of ion channels, channel-linked receptors or ion transporters (I) expressed in cells by:
(a) contacting cells expressing (I) with a signal-generating thallium sensitive agent;
(b) contacting the cells with a candidate modulator (III) or (I), and then with assay buffer containing thallium salt solution; and
(c) detecting or measuring the signal generated by (II) to determine the effect of (III) on the activity of (I).
INDEPENDENT CLAIMS are also included for the following:
(1) a new Cl--free assay buffer for use in thallium sensitive assays; and

(2) a low Cl- cell growth medium containing no more than 2 mM Cl-.

USE - The method is used for detecting and measuring the activity if ion channels, channel-linked receptors, or ion transporters expressed in cells by thallium sensitive assays. The method is useful for identifying a modulator of (I), which is able to activate or inhibit the activity of (I) (claimed). The compounds identified using the method are valuable research tools that can be used to elucidate the biochemistry, physiology, and pharmacology of ion channels, channel-linked receptors or ion transporters in both prokaryotic and eukaryotic systems. The modulators provide lead compounds for diagnostic and therapeutic drug development to treat a variety of disorders, such as, cation channel-associated diseases, diseases associated with channel-linked receptors, antibacterial, antifungal, inflammation modulatory or immunological disorders.

ADVANTAGE - The method provides a simple and convenient optical method to detect cation influx or efflux, preferably flux of thallium ions, allowing the measurement of the activity of an ion channel directly or indirectly by detecting the flux of the ions. The method has no requirements for radioactive reagents and takes advantage of the permeability of thallium ions. The activity of (I) is monitored solely by the thallium flux and is not perturbed by the presence of physiologically relevant ions. There is no requirement for chemical or biochemical modification of (I). The assays can be performed in whole cells, specifically with the use of the new low Cl- cell growth medium and new Cl--free assay buffer. The signal or emission generated by the assay is significantly larger and more robust than that typically obtained using previous optical methods. A change in signal is generated by the presence of a candidate modulator, which facilitates the identification of specific modulatory agents. There a large variety of thallium sensitive agents available. The assay format does not require that the ion channel and/or receptor is to be immobilized on a solid support, and the assay is readily amenable for automation and high-throughput screening.

Dwg.0/7

TECH UPTX: 20021007

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Method: The ion channels comprise cation channels e.g. potassium ion channels, sodium ion channels, or **calcium** ion channels that are permeable to thallium ions. Preferably, the cation ion channels are potassium ion channels, more preferably **calcium**-activated or voltage-gated potassium ion channels, or small conductance **calcium**-activated K+ channels (SK), Maxi-K, HERG or KCNQ channels. Optionally, the cation ion channels are ligand-gated VR1 channels, or non-selective ion channels such as acetylcholine receptors, glutamate receptors such as alpha-amino-3-hydroxy-5-methyl-4-isoxazoleproprionate (AMPA) kainate, or N-methyl-D-aspartate (NMDA) receptors, 5-hydroxytryptamine-gated receptor-channels, ATP-gated (P2X) receptor channels, nicotinic acetylcholine-gated **receptor** -channels, vanilloid **receptors**, **ryanodine receptor**-channels, inositol triphosphate (IP3) receptor-channels, cation channels activated in situ by intracellular cAMP, or cation channels activated in situ by intracellular cGMP. The thallium salt solution comprises a water soluble thallium salt, such as, Tl2SO4, Tl2CO3, TlCl, TlOH, TlNO3, or TlOAc. Preferably the thallium salt is Tl2SO4. The assay buffer is Cl--free and further comprises sodium gluconate, potassium gluconate, **calcium** gluconate, magnesium gluconate, N-(2-OH-ethyl-)piperazine-N'-(2-ethanesulfonic acid) (HEPES), and glucose. The cells are preferably grown in low Cl--cell growth medium, containing no more than 2 mM Cl-. the low Cl- growth medium comprises sodium gluconate, potassium gluconate, MgSO4.7H2O, NaHCO3, **calcium** gluconate, NaH2PO4, HEPES, glucose, 100X vitamins, 50X amino acids, and glutamine. (II) is a thallium sensitive fluorescent agent or thallium sensitive non-fluorescent agent. the thallium sensitive fluorescent agent

is 8-aminonapthalene-1, 3,6-trisulfonate (ANTS), Fluo-4, Fluo-3, PBFI, Phe Green, Magnesium Green, APTRA-BTC, Fluo-4FF, FluoZin-1, FluoZin-2, Mag-Fura Red or BTC. The thallium sensitive non-fluorescent agent is chloride, bromide or iodide. The channel-linked receptors are any one of G-protein coupled receptors (GPCR), metabotropic glutamate receptors, muscarinic acetylcholine receptors, dopamine receptors, and serotonin receptors. The ion transporters are any one of dopamine ion transporters, glutamate ion transporters, seratonin ion transporters, sodium-potassium ATPases, proton-potassium ATPases, sodium/**calcium** exchangers, or potassium-chloride ion co-transporters. The method further involves contacting the cells with extracellular fluorescent quenching compounds after the step of contacting the cells with a signal generating thallium sensitive fluorescent agent. the candidate modulating compounds activate or inhibit the ion channels, channel-linked receptors or ion transporters. The method further comprises adding a stimulus solution to the thallium salt solution. The stimulus solution contains ionophores, KCl, nicotine, acetylcholine, muscarine, or carbamylcholine.
Preferred Buffer: The assay buffer further comprises sodium gluconate, potassium gluconate, **calcium** gluconate, magnesium gluconate, HEPES and glucose.

L4 ANSWER 2 OF 16 WPIDS (C) 2002 THOMSON DERWENT
AN 2002-383097 [41] WPIDS
DNC C2002-107958
TI Use of compound that induces **calcium** ion release through type 1 **ryanodine receptor** to treat obesity.
DC B05
IN BARSOUMIAN, E L; BOONEN, H C M; DIN, N; FLEDELIUS, C; NIELSEN, E B; NISHIMURA, S; RAUN, K; STIDSEN, C E; TULLIN, S; WIELAND, H A
PA (BOEH) BOEHRINGER INGELHEIM INT GMBH; (NOVO) NOVO NORDISK AS
CYC 94
PI WO 2002022122 A1 20020321 (200241)* EN 24p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2000072704 A 20020326 (200251)
ADT WO 2002022122 A1 WO 2000-DK514 20000915; AU 2000072704 A AU 2000-72704 20000915, WO 2000-DK514 20000915
FDT AU 2000072704 A Based on WO 200222122
PRAI WO 2000-DK514 20000915
AB WO 200222122 A UPAB: 20020701
NOVELTY - Use of a compound (I) that induces **calcium** ion (**Ca** 2+) release through type 1 **ryanodine receptor** (Ryr1) for the manufacture of medicaments to treat obesity is new.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:
(1) method for identifying Ryr1 agonists using skeletal muscle microsomes or membrane preparations from cell lines that express Ryr1 recombinantly or endogenously for screening out compounds that affect the binding of 3H-ryanodine to Ryr1; and
(2) method for identifying Ryr1 agonists using cell lines that express Ryr1 recombinantly or endogenously for screening out compounds that induce **Ca** 2+ release through Ryr1.
ACTIVITY - Anorectic.
No biological data given in the source material.
MECHANISM OF ACTION - Ryr1 receptor agonist.
No biological data given in the source material.

USE - For treating obesity, reducing body mass index and increasing energy expenditure.

ADVANTAGE - None stated.

Dwg.0/0

TECH UPTX: 20020701

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Compound: (I) is Ryr1 agonist, ryanodine, anthraquinones, disulfonic stilbene derivatives or adenine nucleotides.

L4 ANSWER 3 OF 16 WPIDS (C) 2002 THOMSON DERWENT
AN 2002-034254 [04] WPIDS
DNN N2002-026399 DNC C2002-009534
TI Diagnosing Alzheimer's disease by comparing first, second raw percentage of cells responding to first, second compounds respectively, to provide ratio index which is compared to predetermined discriminating value.
DC B04 D16 S03 T01
IN ALKON, D L; BANK, B; BHAGAVAN, S; ETCHEBERRIGARAY, R
PA (NEUR-N) NEUROLOGIC INC
CYC 94
PI WO 2001077686 A2 20011018 (200204)* EN 40p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2001055234 A 20011023 (200213)
ADT WO 2001077686 A2 WO 2001-US11060 20010405; AU 2001055234 A AU 2001-55234 20010405
FDT AU 2001055234 A Based on WO 200177686
PRAI US 2000-194626P 20000405
AB WO 200177686 A UPAB: 20020117

NOVELTY - Diagnosing Alzheimer's disease (AD) in patient using integrated scoring system by challenging first, second set of cells of patients with first, second compound to elicit first, second response (FSR), respectively, measuring FSR and calculating first, second raw percent of responding cells; calculating ratio index (RI), determining presence/absence of AD when RI is greater or less than a predetermined value.

DETAILED DESCRIPTION - Diagnosing (M1) the presence or absence of AD in a patient comprising an integrated scoring system involves determining a first value comprising challenging one set of cells from a patient with a first compound to elicit a first response, measuring the first response and calculating a first raw percent of responding cells; determining a second value comprising challenging another set of cells from same patient with a second compound to elicit a second response, measuring the response and calculating a second raw percent of responding cells, one of the first and second responses being increased and the other decreased in AD cells as compared to non-AD cells; calculating the RI by dividing the increased response value by the decreased response value; determining the presence of AD when the RI value is below a predetermined value X; and determining the absence of AD when the RI value is equal to X or higher.

An INDEPENDENT CLAIM is also included for a computer software program for performing (M2) the diagnosis of AD by:

(a) obtaining data comprising first raw percentage of cells of the individual having functional potassium channels, and second raw percentage of cells of the individual responding when contacted by second modulator of intracellular **calcium** release;

(b) calculating RI by either

(i) dividing first raw percentage by the second raw percentage to

provide a RI; or
(ii) dividing the second raw percentage;
(c) comparing the RI to a predetermined discriminating value and for calculation,
(i) scoring the individual as AD negative if the RI exceeds the discriminating value, and as AD positive if the RI does not exceed the discriminating value, or for calculation; and
(ii) scoring the individual as AD positive if the RI exceeds the discriminating value, and as AD negative if the RI does not exceed the discriminating value.
USE - Diagnosing the presence or absence of AD in a patient using an integrated scoring system (claimed).
ADVANTAGE - The method enables diagnosis of individuals as AD positive even when they lack clinical manifestations of AD. The method also identifies the presence of AD in cells from a pre-symptomatic individual. The negative AD diagnosis is not affected by the presence of non-Alzheimer's neurodegenerative conditions. The scoring has sensitivity, specificity and positive predictive value sufficient to provide clinical utility for a particular given population. The method provides greater than 75% (preferably, 95%) sensitivity, specificity, and/or positive predictive value for particular population. The diagnosis detects molecular alterations associated with AD prior to the onset of clinical cognitive or plaque formation symptoms (claimed). The method rapidly and clearly distinguishes between AD patients, normal aged people, and people suffering from other non-Alzheimer's disease neurodegenerative diseases, such as Parkinson's, Huntington's chorea, Wernicke-Korsakoff or schizophrenia. The method provides a simple single-value diagnostic evaluation for AD. The method avoids the need to normalize results for separate assays of **calcium** signaling, permitting use of raw data, which is advantageous in the clinical setting. The methods for diagnosing AD greatly improve the present clinical diagnostic process for AD. The RI is advantageous because it provides a more generally applicable tests, utilizes raw data as opposed to manipulated data, and it provides a more accurate, precise and consistent diagnosis and predictability of AD.
Dwg.0/8

TECH UPTX: 20020117
TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Method: (M1) preferably involves obtaining a sample of cells from an individual; measuring potassium (K+) channel function in a first set of cells of the sample, yielding a first raw percentage of cells having functional potassium channels, the function measurement in non-AD cells being higher than the measurement in AD cells; challenging a second set of cells of the sample with a modulator of intracellular **calcium** (**Ca2+**) release, and measuring a second raw percentage of cells responding to the release modulator that causes an increase in intracellular **calcium** release in AD cells compared to non-AD control cells; calculating a RI by either:
(i) dividing the first raw percentage by the second raw percentage; or
(ii) dividing the second raw percentage by the first raw percentage;
comparing the RI to a pre-determined discriminating value, and for calculation scoring the individual as AD negative if the RI exceeds the discriminating value and as AD positive if the RI does not exceed the discriminating value, or for calculation to scoring the individual as AD positive if the RI exceeds the discriminating value, and as AD negative if the RI does not exceed the discriminating value.
The function is measured by loading first set of cells with radioactive rubidium and measuring rubidium efflux or by measuring channel activity by electrophysiological methods. Preferably, the potassium channel (e.g., 113 pS potassium channel) function measurement involves challenging the first set of cells of the sample with a potassium (K+) channel blocker (e.g.,

tetraethylammonium or charybdotoxin, apamin, dendrotoxin, kalidotoxin, MCD-peptide, scyllatoxin, barium, cesium, leiurotoxin I and noxiustoxin), and measuring the function involves measuring first raw percentage of cells responding to the potassium channel blocker, that causes a measurable response in non-AD cells and a reduced response in AD cells due to defective potassium channel function. The potassium channel blocker measurable value indicates whether potassium channel function is normal or impaired. The response value is preferably obtained by measuring ion flux (e.g., flux of rubidium or potassium or by measuring **calcium** elevation). The modulator of intracellular **calcium** release is an activator of release of intracellular **calcium** such as inositol triphosphate (IP3), **ryanodine receptors** (RYR) or thapsigarin (Tg). Optionally, the modulator of intracellular **calcium** release may be bradykinin, thrombin, bombesin, prostaglandin F2a or vasopressin.

The discriminating value employed in (M1) is 1.1.

The sample of cells is established as a cell line from which the first and second sets are taken. The response is a measure of percent of responding cells per cell line.

The method further involves deriving the discriminating value for a particular pair of potassium channel function measurements and the modulator of intracellular **calcium** release, by calculating the RI using data for known controls and known AD positive individuals.

The diagnosis of AD by the preferred method described above has a performance indicator of about 100% in the samples of a given population such as

(a) specificity (True Negative/True Negative+False Negative);
(b) sensitivity (True Positive/True Positive+False Negative);
(c) positive (True Positive/True Positive+False Negative); or
(d) negative (True Negative/True Negative+False Negative).

Generally the preferred method involves:

(a) (M2); or

(b) obtaining a sample of cells from an individual; measuring a first raw percentage of cells having a functional first **calcium** signaling pathway element in first set of cells, the functionality of the first **calcium** signaling pathway element being reduced in AD cells when compared to control cells, measuring second raw percentage of cells having functional second **calcium** signaling pathway element, the functionality of the second **calcium** signaling pathway element being increased in AD cells compared to control cells, dividing first raw percentage by second raw percentage to provide a ratio index, comparing the RI to a predetermined threshold diagnostic value and scoring the individual as AD positive if the ratio exceeds the threshold diagnostic value and as AD negative if the RI does not exceed the threshold diagnostic value. Preferably, the measurement of the first and/or second raw percentage are performed directly or by indirectly challenging the cells;

(c) obtaining data comprising first and second raw percentage of the cells of the individuals having first and second functional **calcium** signaling pathway elements, respectively; dividing first raw percentage by second raw percentage to provide a RI, comparing the RI to a predetermined threshold diagnostic value and scoring the individual as AD positive if the ratio exceeds the threshold diagnostic value and as AD negative if the RI does not exceed the threshold diagnostic value.

L4 ANSWER 4 OF 16 WPIDS (C) 2002 THOMSON DERWENT
AN 2001-611274 [70] WPIDS
DNC C2001-182572
TI New synthetic or recombinant Maurocalcine or its analogues, useful for preparing an immuno-suppressive medicament, particularly for treating of

pathologies associated with a dysfunction of **calcium** channel subtypes.

DC B04 D16
IN EL-AYEB, M; KHARRAT, R; MABROUK, K; ROCHAT, H; SABATIER, J
PA (CELL-N) CELLPEP SA
CYC 95
PI WO 2001064724 A2 20010907 (200170)* EN 10p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2001062084 A 20010912 (200204)
ADT WO 2001064724 A2 WO 2001-EP2582 20010305; AU 2001062084 A AU 2001-62084 20010305
FDT AU 2001062084 A Based on WO 200164724
PRAI GB 2000-5124 20000303
AB WO 200164724 A UPAB: 20011129
NOVELTY - A synthetic or recombinant Maurocalcine or its bioactive structural analogue (preferably containing the KKKRR motif), is new.
ACTIVITY - Immunosuppressive.
MECHANISM OF ACTION - **Calcium** channel modulator.
No biological data given.
USE - The Maurocalcine, synthetic Maurocalcine or recombinant Maurocalcine, or its bioactive structural analogue is useful for preparing an immuno-suppressive medicament. The medicament is useful for treating of pathologies associated with a dysfunction of **calcium** channel subtypes, including **ryanodine receptors** (all claimed).
Dwg.0/1
TECH UPTX: 20011129
TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: The Maurocalcine may be synthesized by means of an optimized solid-phase method.

L4 ANSWER 5 OF 16 WPIDS (C) 2002 THOMSON DERWENT
AN 2001-432697 [46] WPIDS
DNC C2001-130901
TI Treatment of neuropathies resulting from ischemic reperfusion injury using, e.g. a type 3 **ryanodine receptor** antagonist such as dantrolene, aminodantrolene or azumolene.
DC B03
IN BROWN, G; BULLOUGH, G; MANGAT, H S; BALLOUGH, G
PA (UYSF-N) UNIV SOUTH FLORIDA; (BROW-I) BROWN G; (BULL-I) BULLOUGH G; (MANG-I) MANGAT H S
CYC 94
PI WO 2001041756 A2 20010614 (200146)* EN 28p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW
AU 2001047104 A 20010618 (200161)
US 2001053790 A1 20011220 (200206)
US 6462066 B2 20021008 (200269)
ADT WO 2001041756 A2 WO 2000-US42539 20001204; AU 2001047104 A AU 2001-47104 20001204; US 2001053790 A1 Provisional US 1999-168547P 19991202, US 2000-727707 20001204; US 6462066 B2 Provisional US 1999-168547P 19991202, US 2000-727707 20001204
FDT AU 2001047104 A Based on WO 200141756

PRAI US 1999-168547P 19991202; US 2000-727707 20001204
AB WO 200141756 A UPAB: 20011206
NOVELTY - A compound which decreases cytosolic **calcium** ion concentration is used to treat neuropathies resulting from ischemic reperfusion injury.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for:
(A) treatment of neuronal reperfusion injury in a patient with ischemic neuropathy, comprising administration of a composition comprising
(i) a compound which decreases cytosolic **Ca2+** concentration caused by the injury; and
(ii) a carrier;
(B) decreasing reperfusion damage to the retina of a patient, comprising administration of a composition comprising
(i) a salt of a compound which is an antagonist of type 3 **ryanodine receptor** and which reduces the increase in cytosolic **Ca2+** concentration incident to reperfusion injury; and
(ii) a carrier;
(C) treatment of ischemic retinopathy reperfusion injury in mammals, comprising administration of
(i) a protective agent which inhibits intracellular **calcium** -mediated retinal cell damage; and
(ii) a carrier;
(D) prevention of ischemic neuropathy reperfusion injury in mammals, comprising administration of a salt of dantrolene and/or a salt of aminodantrolene; and
(E) reducing reperfusion damage in a patient suffering from, or at risk of, ischemia, comprising administration of a composition comprising
(i) a carrier; and
(ii) a salt of a compound which inhibits intracellular release of **calcium** ions.
ACTIVITY - Neuroprotective; Vasotropic; Ophthalmological; Cerebroprotective.
MECHANISM OF ACTION - Type 3 **ryanodine receptor** antagonist.
USE - The processes are useful for treating or preventing neuropathies resulting from ischemic reperfusion injury. These include optic ischemic neuropathy or stroke.
ADVANTAGE - The active agents block release of intracellular **calcium** stores during reperfusion by antagonism of the **ryanodine receptor**.
Dwg.0/7

L4 ANSWER 6 OF 16 WPIDS (C) 2002 THOMSON DERWENT
AN 2001-374334 [39] WPIDS
DNC C2001-114315
TI Analyzing molecular events in the brain, especially hippocampal tissue involves hybridizing isolated brain mRNA to oligonucleotide array, clustering groups of genes and analyzing alterations of expression levels of genes.
DC B04 D16
IN CAO, Y; MODY, M; TSIEN, J Z
PA (AFFY-N) AFFYMETRIX INC; (UYPR-N) UNIV PRINCETON
CYC 94
PI WO 2001030973 A2 20010503 (200139)* EN 53p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW

AU 2001024701 A 20010508 (200149)
EP 1226280 A2 20020731 (200257) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
ADT WO 2001030973 A2 WO 2000-US41515 20001025; AU 2001024701 A AU 2001-24701 20001025; EP 1226280 A2 EP 2000-988496 20001025, WO 2000-US41515 20001025
FDT AU 2001024701 A Based on WO 200130973; EP 1226280 A2 Based on WO 200130973
PRAI US 2000-227639P 20000824; US 1999-161337P 19991025
AB WO 200130973 A UPAB: 20010716
NOVELTY - Analyzing (M1) genome-wide molecular events occurring in brain tissue involves hybridizing isolated brain mRNA to an oligonucleotide array, clustering groups of genes together using self-organizing map analysis, and analyzing alterations of expression levels of genes.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a brain development related nucleic acid molecule (I) comprising a defined sequence;

(2) isolating (M1) protein sequences involves assembling a hybridization reaction mixture containing one or more of isolated nucleic acid molecules in single stranded form, and a test sample that comprises the corresponding protein coding sequence in a single-stranded form, under conditions enabling hybridization of the isolated nucleic acid molecule and the protein sequence, by forming a double stranded nucleic acid molecule, separating the double stranded molecule comprising the isolated nucleic acid and the protein coding sequence and cloning the protein coding sequence;

(3) an isolated protein (II) produced by expression of the protein coding sequences isolated by (M1);

(4) antibodies immunologically specific for (II);

(5) a recombinant DNA molecule comprising a protein coding sequence produced by (M1), operably linked to a vector for transforming cells;

(6) screening (M1) for candidate drugs which induce or inhibit expression of genes in the hippocampus involves contacting a hippocampal cell with a candidate drug for sufficient time for detectable expression of a gene and assaying for the amount of expression in the cell (II), or two or more of the following genes (III) e.g. cyclin-dependent kinase regulatory subunit 2, cyclin B2, cyclin G2, G1/S-specific cyclin D2, D-type G1 cyclin catalytic subunit (PSK-J3/CDK4), cell division protein kinase 4(PSK-J3), D-type cyclin (CYL2), GADD45 (growth arrest and DNA damage induced protein), WW-domain binding protein-1, elongation factor-1-alpha , elongation factor-1- gamma , elongation factor-2 (EF-2), initiation factor 2 associated 67Kd glycoprotein, tubulin beta -1 chain, tubulin alpha -1, tubulin alpha -4, tubulin alpha -5, tubulin alpha -6, tubulin alpha -8, tubulin beta -3, tubulin beta -4 (class III), tubulin alpha -2, tubulin M- alpha -3, tubulin M- beta -5, CCT eta subunit (chaperonin containing TCP-1), CCT epsilon subunit (chaperonin containing TCP-1), CCT eta subunit (chaperonin containing TCP-1), CCT epsilon / theta subunit (chaperonin containing TCP-1), fatty acid synthase, Lipoprotein lipase precursor, squalene epoxidase, cell division control protein 4, transcription factor Sox-M, phosphofructokinase (PFK), pyruvate kinase, glucose-6-phosphate isomerase, fructose bisphosphate aldolase A, triose phosphate isomerase, sodium/potassium transporting ATPase beta -1 chain, sodium/potassium transporting ATPase alpha -2 chain, **calcium** -transporting ATPase sarcoplasmic reticulum type, and **calcium** -transporting ATPase endoplasmic reticulum type class 2. The expression of the genes in the cell is assayed before and after the cell has been contacted with the test substance, and in which the candidate drug is identified if it increases or decreases expression of one or more of the genes; and

(7) treating a disease involves administering to a diseased patient,

(III) or a polypeptide which competes with the polypeptide encoded by one of the above genes for its ligand, substrate or receptor.

ACTIVITY - Cytostatic; neuroprotective.

MECHANISM OF ACTION - Gene therapy.

USE - (II) is useful for treating a disease in a patient which involves administering (II) or a polypeptide which competes with the polypeptide encoded by (III) for its ligand, substrate or receptor (claimed). The proteins encoded by the novel genes provide novel biological targets for neuronal disorders associated with the aberrant expression of brain development-related nucleic acids. The novel genes are also useful as probes to determine the expression pattern of unknown cells or to identify a sample of tissue or cell as belonging to the appropriate developmental stage or organ source, to identify human homologues, as tools in the development of therapeutic drugs for treating neuronal degeneration diseases, nerve injuries, aging and cancer, as molecular expression markers, especially hippocampal tissue to confirm tissues of identifications made on the basis of morphological criteria, monitoring disease progression involving brain tissue and for monitoring the efficacy of certain drug treatments. Neuronal disorders can also be diagnosed by determining from a sample derived from a subject, an abnormally decreased or increased level of the novel genes on corresponding mRNA. The nucleic acid sequences are also useful as primers to amplify corresponding full length nucleic acids.

ADVANTAGE - The cluster method accurately reflects the potential underlying molecular and genetic programs during the hippocampal development.

Dwg.0/4

TECH UPTX: 20010716

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Gene: Cyclin-dependent kinase regulatory subunit 2, cyclin B2, cyclin G2, G1/S-specific cyclin D2, D-type G1 cyclin catalytic subunit (PSK-J3/CDK4), cell division protein kinase 4(PSK-J3), D-type cyclin (CYL2), GADD45 (growth arrest and DNA damage induced protein), oral tumor suppressor homolog (Doc-1), p53 cellular tumor antigen, DNA topoisomerase II, proliferating cell nuclear antigen, RNA polymerase I, 40 kD subunit, RNA helicase and RNA-dependent ATpase from DEAD box family, U2-snRNPb (pRNP11), U6-snRNA-associated protein, unwinding protein 1-, pre-mRNA splicing factor SRP75, myoblast cell surface antigen 24.1D5, histone H2A.X, replication-dependent histone H2A.1, H1 histone subtype H1(0), histone H2A.Z, J kappa RS-binding protein, transcription factor BTF3, neurogenin-2 (ngn2), myelin transcription factor 1, CAAT-box DNA binding protein subunit B (NF-YB), WW-domain binding protein-1, elongation factor-1-alpha, elongation factor-1-gamma, elongation factor-2 (EF-2), initiation factor 2 associated 67Kd glycoprotein, translational initiation factor 2 beta subunit (EIF-2), ubiquitin-conjugating enzyme E2, 60S ribosomal protein A52, ribosomal protein L5, ribosomal protein L8(RPL8), 60S ribosomal protein L9, ribosomal protein L12 (RPL12), 60S ribosomal protein L13A, ribosomal protein L18(RPL18), ribosomal protein L19, ribosomal protein L30, 60S ribosomal protein L23, 60S ribosomal protein L32, 60S ribosomal protein L34, 60S ribosomal protein L37, ribosomal protein S8, 40S ribosomal protein L24, ribosomal protein Ke-3, actin, cytoplasmic 1 (beta actin), actin-1, actin-3, cytoskeletal gamma actin, tubulin M-alpha-3, tubulin beta-1 chain, tubulin alpha-1, tubulin alpha-4, tubulin alpha-5, tubulin alpha-6, tubulin alpha-8, tubulin beta-3, tubulin beta-4 (class III), tubulin alpha-2, tubulin M-alpha-3, tubulin M-beta-5, CCT eta subunit (chaperonin containing TCP-1), CCT epsilon subunit (chaperonin containing TCP-1), CCT eta subunit (chaperonin containing TCP-1), CCT epsilon/theta subunit (chaperonin containing TCP-1), TCP-1 chaperonin cofactor A, valyl-tRNA synthetase, threonyl-tRNA synthetase, ubiquitin-conjugating enzyme (UbcM2), ubiquitin carboxyl-terminal hydrolase,

ubiquitin-activating enzyme E1-X, cysteine protease, collagen alpha-1, type IV (col4a-1), fibronectin (FN), tenascin, gamma-actin, L1-like protein, neural cell adhesion molecule, (NCAM), neural cell adhesion molecule L1 (NCAM-L1), neurophilin, neural cadherin (N-cadherin), membrane-type matrix metalloproteinase 1, brain fatty acid-binding protein (B-FABP), fatty acid synthase, Lipoprotein lipase precursor, squalene epoxidase, Farnesyl pyrophosphate synthetase, keratinocyte lipid-binding protein, myelin gene expression factor (MEF-2), N-glycan alpha 2,8-sialyltransferase, clathrin, light chain B, synaptogamin I/65, UNC-18 homologue, vesicle associated membrane protein (VAMP2), synaptophysin (major synaptic vesicle protein P38), neuronal pentraxin 1, N-methyl-D-aspartate receptor-glutamate binding chain, neurogranin (protein kinase C substrate 7.5 kD), alpha-SNAP protein, **calcium** -activated potassium channel, potassium channel, beta-subunit, brain neurotensin receptor, acetylcholine receptor-interacting protein (AIP), fractalkine, cholecystokinin, brain derived neurotrophic factor (BDNF), glutamate receptor 1 (GluR1), glutamate receptor 2 (GluR2), SH3-containing protein (SH3P4), SH3P9, C-H-Ras, Ras-related protein RAB-3A, mitogen activated protein kinase (erk-1), receptor-type tyrosine kinase, focal adhesion kinase, calcineurin, phospholipase C beta 1, diglyceride kinase, RhoB, protein kinase C, cell division cycle homolog (CDC25), elongation factor(alpha-CMS1), growth factor-induced protein (zif/268), DNA-binding protein (Smbp-2), protooncogene DBL, transcriptional activator FE6J, cell division control protein 4, transcription factor Sox-M, phosphofructokinase (PFK), pyruvate kinase, glucose-6-phosphate isomerase, fructose bisphosphate aldolase A, triose phosphate isomerase, gamma enolase (2-phospho-D-glycerate hydrolyase), alpha- enolase (2-phospho-D-glycerate hydrolase), glycogen phosphorylase, glycerol kinase, NADH-ubiquinone oxidoreductase chain 49 kD subunit, NADH-ubiquinone oxidoreductase AGGG subunit precursor, cytochrome c oxidase subunit VIII precursor (Cox81), succinate dehydrogenase, malate dehydrogenase, lactate dehydrogenase-B, glycerophosphate dehydrogenase, antioxidant protein 2 (AOP2), **ryanodine receptor** type 2, vacuolar adenosine triphosphatase, subunit B, vacuolar adenosine triphosphatase, subunit E, voltage-dependent anion channel 1, sodium/potassium transporting ATPase beta-1 chain, sodium/potassium transporting ATPase alpha-2 chain, **calcium**-transporting ATPase sarcoplasmic reticulum type, Vacuolar ATP synthase subunit C, vacuolar ATP synthase subunit AC45, vacuolar ATP synthase 16 KD proteolipid subunit, and **calcium**-transporting ATPase endoplasmic reticulum type class 2.

Preferred Method: The brain mRNA employed in (M1) is an hippocampal mRNA.

Preferred Nucleic Acid: (I) comprises a sequence selected from the following accession numbers: having an accession number of TC14224, TC14254, TC14312, TC14325, TC14329, TC14435, TC14474, TC14629, TC14635, TC14704, TC14731, TC14735, TC14762, TC14763, TC14785, TC14788, TC14810, TC14823, TC14941, TC14972, TC14982, TC15012, TC15118, TC15133, TC15141, TC15204, TC15267, TC15448, TC15584, TC15665, TC15831, TC15974, TC16153, TC16205, TC16355, TC16494, TC16651, TC16708, TC17122, TC17275, TC17320, TC17874, TC17980, TC18222, TC18241, TC18400, TC18401, TC18687, TC18688, TC18708, TC18783, TC18804, TC18850, TC18869, TC18884, TC19058, TC19062, TC19069, TC19082, TC19105, TC19136, TC19211, TC19521, TC19732, TC19823, TC19926, TC19967, TC20099, TC20539, TC20803, TC21082, TC21205, TC21335, TC21412, TC21626, TC21685, TC21976, TC22202, TC22386, TC22448, TC22529, TC22542, TC22668, TC22669, TC22696, TC22785, TC23211, TC23244, TC23261, TC23542, TC23801, TC23956, TC24584, TC26547, TC26624, TC26682, TC27097, TC27333, TC27344, TC27510, TC27517, TC27528, TC27570, TC27571, TC27572, TC27573, TC27712, TC27850, TC27894, TC27963, TC28142, TC28255, TC28416, TC28417, TC28666, TC28824, TC28847, TC28859, TC28885, TC29042, TC29129, TC29216, TC29328, TC29385, TC29394, TC29445, TC29454, TC29479, TC29708,

TC29810, TC30188, TC30208, TC30378, TC30379, TC30391, TC30530, TC30545, TC30555, TC30650, TC30755, TC30788, TC30805, TC30906, TC30918, TC30981, TC30987, TC31022, TC31051, TC31091, TC31128, TC31250, TC31334, TC31339, TC31349, TC31386, TC31671, TC31678, TC31686, TC31729, TC31755, TC31774, TC31783, TC31827, TC31864, TC31882, TC31917, TC31921, TC32043, TC32074, TC32106, TC32222, TC32250, TC32296, TC32304, TC32321, TC32325, TC32339, TC32438, TC32456, TC32559, TC32602, TC32713, TC32808, TC32829, TC32833, TC32980, TC33002, TC33009, TC33036, TC33177, TC33178, TC33179, TC33208, TC33209, TC33231, TC33232, TC33244, TC33290, TC33306, TC33377, TC33378, TC33384, TC33396, TC33407, TC33529, TC33531, TC33738, TC33757, TC33765, TC33775, TC33788, TC33816, TC33823, TC33849, TC33852, TC33859, TC33866, TC33882, TC33985, TC34265, TC34289, TC34379, TC34965, TC34983, TC35017, TC35086, TC35131, TC35597, TC35648, TC35734, TC35822, TC35823, TC35874, TC35937, TC35974, TC36080, TC36082, TC36142, TC36344, TC36565, TC36683, TC36730, TC36740, TC36797, TC36816, TC36917, TC36970, TC37016, TC37019, TC37101, TC37186, TC37226, TC37230, TC37266, TC37268, TC37366, TC37388, TC37411, TC37468, TC37472, TC37670, TC37689, TC37720, TC37721, TC37793, TC37904, TC38039, TC38045, TC38052, TC38091, TC38092, TC38136, TC38142, TC38247, TC38281, TC38297, TC38377, TC38446, TC38523, TC38552, TC38590, TC38627, TC38806, TC38862, TC38867, TC39079, TC39101, TC39196, TC39214, TC39296, TC39303, TC39305, TC39334, TC39418, TC39420, TC39605, TC39644, TC39809, TC39826, TC39827, TC39868, TC39877, TC39895, TC39990, TC40025, TC40265, TC40450, TC40459, TC40494, TC40580, TC40603, TC40618, TC40687, TC40689, TC40704, TC40734, TC40780, TC40817, TC40833, TC40840, TC40879, TC40931, TC40975, TC41027, TC41069, TC41106, TC41175, TC41197, TC41200, TC41472, TC41499, TC41551, TC41561, TC41569, TC41588, TC41818, TC41859, TC41872, TC41992 or TC42517.

L4 ANSWER 7 OF 16 WPIDS (C) 2002 THOMSON DERWENT
AN 2001-226543 [23] WPIDS
DNC C2001-067595
TI Use of new and known amine compounds for stimulating neuronal activity for treating e.g. Alzheimer's and Parkinson's disease, neuralgias and multiple sclerosis.
DC B03 B05
IN BRUMBY, T; MCDONALD, F; SCHNEIDER, H
PA (SCHD) SCHERING AG; (VERT-N) VERTEX PHARM INC
CYC 94
PI WO 2001012622 A1 20010222 (200123)* EN 63p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW
DE 19939707 A1 20010329 (200125)
AU 2000069137 A 20010313 (200134)
EP 1204657 A1 20020515 (200239) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
ADT WO 2001012622 A1 WO 2000-US22617 20000818; DE 19939707 A1 DE 1999-19939707 19990818; AU 2000069137 A AU 2000-69137 20000818; EP 1204657 A1 EP 2000-957534 20000818, WO 2000-US22617 20000818
FDT AU 2000069137 A Based on WO 200112622; EP 1204657 A1 Based on WO 200112622
PRAI US 1999-150568P 19990825; DE 1999-19939707 19990818
AB WO 200112622 A UPAB: 20010425
NOVELTY - Use of new and known amine compounds (I) is claimed for stimulating neuronal activity.
DETAILED DESCRIPTION - Use of new and known amine compounds (I) and their salts is claimed for stimulating neuronal activity.

X = S, SO, SO2, NH, or NR5;
Y = SO2, COCO, CONH, CSNH, COCOO, COCONH, COO, or SO2NH, CO or a bond;
R1 = H, Ar, or 1-7C alkyl, 2-7C alkenyl, 3-7C cycloalkyl, or 5-7C cycloalkenyl (all optionally substituted by Ar or E);
R2 = 1-6C alkyl (optionally substituted by phenyl or halophenyl);
R3 = 1-6C alkyl, 2-6C alkenyl, 3-7C cycloalkyl, 5-7C cycloalkenyl, or cyclohexylmethyl (all optionally substituted by 1 or 2 Ar), or
NR2R3 = 5-7 membered heterocyclyl (optionally substituted by 1-4C alkyl or hydroxy);
R4, R5 = Ar, 1-9C alkyl, haloalkyl, or 2-9C alkenyl (all optionally substituted by 1 or 2 Ar, 3-7C cycloalkyl, or 5-7C cycloalkenyl);
Ar = 6-12C mono- or bi- cyclic aryl or partially hydrogenated aryl (optionally containing 1-4 N, S or O heteroatoms and optionally substituted by 1-3 E) and
E = halo, OH, nitro, cyano, CF3, OCF3, amino, phenyl, methylenedioxy, phenoxy, benzyloxy, 1-4C alkyl or 1-4C alkoxy.
An INDEPENDENT CLAIM is included for new compounds (I), provided that:
(a) when Y is SO2, R1 is not H;
(b) Y is not CO or a bond;
(c) when X = NR5 and YR1 = tosyl, then R2-R5 are not all methyl;
(d) when X = SO, Y = CONH, R1 and R2 = benzyl, and R3 = vinyl, then R4 is not n-butyl;
(e) when X = NR5 and YR1 = tosyl, and NR2R3 together = 6-7 membered saturated azacyclyl, R4 and R5 are not both n-propyl and
(f) when X = NR5, Y = CSNH, R1 = p-tolyl, and R3 = phenyl, then R2, R4 and R5 are not all methyl.
INDEPENDENT CLAIMS are included for the preparation of (I).
ACTIVITY - Neuroprotective; nootropic; vasotropic; cerebroprotective; analgesic; muscular.
MECHANISM OF ACTION - (I) Increase cytoplasmic **Ca2+** concentration and bind to **ryanodine receptors**.
Tests are described, but no results are given.
USE - Used for treating neurodegeneration, promoting neuronal regeneration, treating neurological diseases and stimulating neurite growth, particularly for treating amyotrophic lateral sclerosis, Alzheimer's and Huntington's diseases, ischemia, strokes, multiple sclerosis, peripheral neuropathies, neuralgias, muscular atrophies and Guillain-Barre syndrome. (I) Are also used for treating trigeminal neuralgia, Collet-Sicard and Tourette's syndromes, Bell's palsy, myasthenia gravis, muscular dystrophy and damage, peripheral and central myelin disorders, Parkinson's disease, trauma, herniated, ruptured or prolapsed invertebrae disk syndrome, cervical spondylosis, plexus disorders, thoracic outlet destruction syndrome, motor neuron diseases, sciatic crush, neuropathy associated with diabetes, spinal cord injuries, facial nerve crush and other trauma and chemotherapy and other medication induced neuropathies.
ADVANTAGE - (I) do not bind to the FK506 binding protein or have immunosuppressive activity responsible for undesirable side effects of prior art drugs. (I) can pass through the blood/brain barrier and are stable metabolically. (I) interact with a **calcium** ion release channel in the endoplasmic reticulum of nerve cells.
Dwg.0/0

TECH UPTX: 20010425
TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: Preparation of (I) comprises e.g. reacting a protected amine compound of formula (II) with H-XaR4, optionally oxidizing to sulfoxide or sulfone, cleaving off P and introducing Y-R1.
A = a reactive leaving group and

P = a protecting group.

L4 ANSWER 8 OF 16 WPIDS (C) 2002 THOMSON DERWENT
AN 2000-543472 [49] WPIDS
DNC C2000-161727
TI New heteroaromatic compounds, useful e.g. in the treatment of Parkinson's, Alzheimer's and Huntington's diseases, stimulate neurite growth.
DC B03 B04
IN BRUMBY, T; MCDONALD, F; OTTOW, E; SCHNEIDER, H
PA (SCHD) SCHERING AG; (VERT-N) VERTEX PHARM INC
CYC 90
PI WO 2000046222 A1 20000810 (200049)* EN 37p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW
DE 19905256 A1 20000810 (200049)
AU 2000026378 A 20000825 (200059)
US 6284779 B1 20010904 (200154)
ADT WO 2000046222 A1 WO 2000-US2660 20000203; DE 19905256 A1 DE 1999-19905256 19990203; AU 2000026378 A AU 2000-26378 20000203; US 6284779 B1 Provisional US 1999-126007P 19990324, US 2000-496278 20000201
FDT AU 2000026378 A Based on WO 200046222
PRAI US 2000-496278 20000201; DE 1999-19905256 19990203; US 1999-126007P 19990324
AB WO 200046222 A UPAB: 20001006
NOVELTY - Heteroaromatic compounds (I) and their salts are new.

DETAILED DESCRIPTION - Heteroaromatic compounds of formula (I) and their salts are new.

R1 = H, Ar', 1-7C alkyl, 2-7C alkenyl, 3-7C cycloalkyl or 5-7C cycloalkenyl (all optionally substituted by Ar' or E);

Y' = C(O)C(O), SO2, -C(O)NH-, -C(S)NH--, C(O)C(O)O, C(O)C(O)NH, C(O)O or SO2NH;

R2 = 1-6C alkyl (optionally substituted by phenyl or halogenated phenyl);

R3 = 1-6C alkyl, 2-6C alkenyl, 3-7C cycloalkyl, 5-7C cycloalkenyl, cyclohexylmethyl (all optionally substituted by 1 - 2 Ar'); or

NR2R3 = 5-7 membered heterocyclyl (optionally unsaturated and optionally substituted by 1-4C alkyl or OH);

X = 5-membered heteroaryl with 1 - 3 N, O or S;

R4 = 1-9C alkyl or 2-9C alkenyl (both optionally substituted by 1 - 2 Ar', 3-7C cycloalkyl or 5-7C cycloalkenyl), Ar', 3-7C cycloalkyl or 5-7C cycloalkenyl;

Ar' = 6-12C mono- or bicyclic aromatic compound containing 0 - 4 N, S or O and optionally partially hydrogenated and optionally substituted by 1 - 3 E;

E = halogen, OH, NO2, CF3, CN, OCF3, NH2, phenyl, methylenedioxy, phenoxy, benzyloxy, 1-4C alkoxy or 1-4C alkyl.

INDEPENDENT CLAIMS are also included for:

(1) a pharmaceutical agent containing (I) a neurotrophic factor; and

(2) preparation of (I).

ACTIVITY - Neuroprotective; nootropic; vasotropic; analgesic; cerebroprotective.

Assays are described but no activity data is given.

MECHANISM OF ACTION - It is believed that (I) increase cytoplasmic **Ca2+** concentrations by interaction with a **calcium** release channel (e.g. the **ryanodine receptor** or the inositol 1,4,5-triphosphate receptor) in the endoplasmic reticulum of the

nerve cell.

USE - (I) are used in the treatment and prevention of neurodegeneration, for stimulation of neuronal regeneration, for the treatment of neurological diseases and for the stimulation of neurite growth e.g. in the treatment of Parkinson's, Alzheimer's and Huntington's diseases, amyotrophic lateral sclerosis, ischemia, stroke, multiple sclerosis, peripheral neuropathy, neuralgia, muscular atrophy and Guillain-Barre syndrome (all claimed), as well as e.g. peripheral neuropathies, trigeminal and glossopharyngeal neuralgia, Bell's Palsy, Tourette's syndrome, muscular trauma, central and peripheral myelin disorders.

ADVANTAGE - (I) possess neuronal activity but do not bind to FKBP. They are devoid of multi-drug resistance reversal activity. They are metabolically stable and pass through the blood-brain barriers and stimulate neurite growth on their own or in the presence of other neuronal growth factors.

Dwg.0/0

TECH UPTX: 20001006

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Agent: The neurotrophic factor is selected from IGF (insulin-like growth factor)-1, gIGF-1, Des(1-3)IGF-1, aFGF (fibroblast growth factor), bFGF, PDGF (platelet derived growth factor), BDNF (brain derived neurotrophic factor), CNTF (undefined), GDDNF (undefined), TN-3 (undefined), NT (neurotriphin)-4/5 or preferably NGF (nerve growth factor).

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: Claimed preparation of (I) comprises cleaving off the amino-protecting group, P', from a compound of formula (II) and introducing Y'-R1, followed by optional separation of the isomers and salt formation.

L4 ANSWER 9 OF 16 WPIDS (C) 2002 THOMSON DERWENT
AN 2000-451225 [39] WPIDS
CR 1999-287249 [24]
DNC C2000-137443
TI Stimulating growth of damaged neurons in spinal cord, and neurites of a patient suffering from Alzheimer's, Parkinson's disease, or physical damage to spinal cord, involves administering FK506 binding protein (FKBP)-binding compound.
DC B04
IN DAWSON, T M; GEORGE, E B; LYONS, W E; SNYDER, S H; STEINER, J P
PA (UYJO) UNIV JOHNS HOPKINS SCHOOL MEDICINE
CYC 1
PI US 6080753 A 20000627 (200039)* 30p
ADT US 6080753 A Cont of US 1994-229601 19940412, US 1997-931070 19970915
FDT US 6080753 A Cont of US 5898029
PRAI US 1994-229601 19940412; US 1997-931070 19970915
AB US 6080753 A UPAB: 20000818

NOVELTY - Stimulating growth of damaged peripheral nerves, damaged spinal cord neurons, motor neurons, damaged neurons, or neurites on neuronal cells, in a patient suffering from Alzheimer's or Parkinson's disease or physical damage to spinal cord, comprising administering a compound having an affinity for FKBP (FK506- binding protein), is new.

ACTIVITY - Neuroprotective; nootropic; antiParkinsonian. The neurite extension enhancement activity of FK506 was tested in vitro. PC-12 cells maintained in a standard culture medium were plated at 1 multiply 105 in 35 mm culture vessels coated with rat tail collagen at 5 micro g/cm2 for differentiation in nerve growth factor. The cells were allowed to attach before replacing the medium with Dulbecco's modified eagle medium (DMEM) supplemented with 2 % fetal horse serum, 1 % fetal calf serum, NGF (nerve growth factor) and/or FK506 or rapamycin. For quantitation of neurite outgrowth, random photographs were made (3-4 per well), and process

bearing neurons were counted with processes being greater than 5 micro m. Neurites were identified and counted from approximately 100 cells per photograph. Results show that NGF potently stimulates neurite outgrowth with half-maximal stimulation at 1 ng/ml and maximal augmentation at about 50-100 ng/ml. FK506 (100 nM) markedly augments the effect of NGF by increasing sensitivity to NGF. FK506 reduces by 20-50 fold the NGF concentration needed to elicit maximal outgrowth. Half maximal outgrowth in the absence of FK506 occurs at 5 ng/ml NGF and in the presence of FK506 at 0.1 ng/ml NGF. At maximal concentrations of NGF (10-100 ng/ml), FK506 fails to produce additional neurite outgrowth. In the presence of a submaximal concentration of NGF (1 ng/ml) FK506 at 1 nM elicits the same maximal outgrowth observed with 50 ng/ml NGF. Half maximal effects of FK506 occur at approximately 100 pM. In the absence of NGF, FK506 fails to elicit neurite outgrowth.

MECHANISM OF ACTION - **Calcium** dependent phosphatase, calcineurin and **calcium** release channel, the **ryanodine receptor** regulator.

USE - The methods are used for stimulating growth of damaged neurons in the spinal cord, especially peripheral nerves, growth of motor neurons, or growth of neurites on neuronal cells in a patient suffering from Alzheimer's or Parkinson's disease or physical damage to spinal cord (claimed).

Dwg.0/13

TECH UPTX: 20000818

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Compound: The compound having an affinity for FKBP is FK506 or rapamycin.

TECHNOLOGY FOCUS - BIOLOGY - Preferred Method: The growth of motor neurons is stimulated in a patient with amyotrophic lateral sclerosis and the growth of neurites from neuronal cells is stimulated in the case of a patient who is at risk of stroke or a neurodegenerative disease.

L4 ANSWER 10 OF 16 WPIDS (C) 2002 THOMSON DERWENT
AN 2000-246571 [21] WPIDS
DNC C2000-074642
TI Identifying compounds capable of modulating cellular response useful for treating Alzheimer's disease and cardiac disorders, involves incubating compound with cell expressing Homer protein and cell-surface receptor.
DC B04 D16
IN BENEKEN, J; LANAHAN, A A; LEAHY, D; TU, J C; WORLEY, P F; XIAO, B
PA (UYJO) UNIV JOHNS HOPKINS SCHOOL MEDICINE
CYC 89
PI WO 2000011204 A2 20000302 (200021)* EN 171p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZA ZW
AU 9957798 A 20000314 (200031)
EP 1105734 A2 20010613 (200134) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
JP 2002523056 W 20020730 (200264) 170p
ADT WO 2000011204 A2 WO 1999-US18973 19990818; AU 9957798 A AU 1999-57798 19990818; EP 1105734 A2 EP 1999-945113 19990818, WO 1999-US18973 19990818; JP 2002523056 W WO 1999-US18973 19990818, JP 2000-566456 19990818
FDT AU 9957798 A Based on WO 200011204; EP 1105734 A2 Based on WO 200011204; JP 2002523056 W Based on WO 200011204
PRAI US 1999-138494P 19990609; US 1998-97334P 19980818; US 1999-138426P

19990609; US 1999-138493P 19990609

AB WO 200011204 A UPAB: 20000502

NOVELTY - Identifying a compound (I) capable of modulating a cellular response mediated by cell surface receptor or intracellular receptor, comprising incubating (I) with a cell expressing a Homer protein and a cell surface receptor or an intracellular protein, is new.

DETAILED DESCRIPTION - (I) comprises:

(a) incubating (I) and a cell expressing a cell surface receptor or an intracellular protein under conditions allowing interaction;

(b) exposing the cell to a cell-surface receptor ligand or to conditions that activates the intracellular protein; and

(c) comparing a cellular response in the cell with a cell not incubated with (I) and identifying (I) that modulates the cellular response.

INDEPENDENT CLAIMS are also included for the following:

(1) a method of identifying a compound that modulates receptor-activated **calcium** mobilization, comprising:

(a) incubating a compound and a cell expressing a Homer protein under conditions allowing interaction;

(b) exposing the cell to conditions sufficient to activate **calcium** mobilization; and

(c) comparing the cellular response in the cell with a cell not incubated with the compound;

(2) a method of identifying a compound that inhibits Homer protein activity, comprising:

(a) designing a potential inhibitor for Homer protein activity based upon the crystal structure co-ordinates of Homer protein binding domain, that will form non-covalent bonds with amino acids in a Homer binding site;

(b) synthesizing the inhibitor; and

(c) determining whether the inhibitor inhibits Homer protein activity;

(3) a method of identifying a compound that affects the formation of cell surface receptors into clusters, comprising:

(a) incubating a compound and a cell expressing a Homer protein and a shank protein under conditions allowing interaction;

(b) determining the effect of the compound on the formation of cell surface receptors into clusters; and

(c) identifying the compound by comparing the formation of cell-surface receptors into clusters with the formation of clusters in a cell not incubated with the compound;

(4) an isolated nucleic acid encoding Homer protein 1b, 1c, 2a, 2b or 3 having sequences fully defined in the specification;

(5) an isolated Homer protein 1b, 1c, 2a, 2b or 3 having sequences fully defined in the specification;

(6) an isolated peptide having one of sequence PPXXFR where R can be arginine, nothing or other amino acid residue;

(7) an isolated peptide having a sequence ALTPPSPFRD;

(8) an isolated nucleic acid encoding a Homer interacting protein having one of three sequences fully defined in the specification;

(9) an isolated Homer interacting protein having either of two sequences fully defined in the specification;

(10) a substantially purified polypeptide containing a proline-rich region that binds to a polypeptide of the Homer family; and

(11) a transgenic non-human animal having a transgene that expresses Homer protein 1a chromosomally integrated into the germ cells of the animal.

ACTIVITY - Anticonvulsant; nootropic; cerebroprotective; neuroleptic; neuroprotective.

MECHANISM OF ACTION - Regulator of receptor-activated **calcium**

mobilization and neurotransmitter receptor clustering at synapses.
USE - Identified compounds which modulate Homer protein activity are useful for treating disorders associated with glutamate receptors such as epilepsy, glutamate toxicity, memory disorders, disorders or learning, stroke, schizophrenia, Alzheimer's disease, tissue degeneration and disorders of brain development and also for treating disorders associated with Homer protein activity which includes cardiac, muscular, vascular, neurological, psychiatric, renal, uterine and bronchial tissue disorders and for affecting the natural aging process (claimed). Compounds identified by (II) are useful for modulating receptor-mediated **calcium** mobilization, by exposing a cell to the compound to modulate **calcium** mobilization that normally occurs when the cell is exposed to a ligand, typically an agonist or antagonist of metabotropic glutamate receptors, to activate an intracellular signaling pathway, especially an inositol triphosphate signaling pathway (claimed).
Dwg.0/47

TECH UPTX: 20000502
TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred method: The cell-surface receptor in the novel method is a glutamate receptor preferably group I metabotropic or ionotropic glutamate receptor. The metabotropic glutamate receptor is preferably receptor 1alpha or 5 and the ionotropic glutamate receptor is preferably NMDA glutamate receptor of the class NR2B or NR2D. The cellular response is preferably an increase or decrease in **calcium** mobilization. In the method of (2), the crystal structure coordinates of the Homer protein binding domain are obtained by computational analysis from a Homer protein crystal having orthorhombic space group symmetry P212121 with a = 33.79, b = 51.40 and c = 66.30 Angstrom. The inhibitor is designed to form hydrogen bonds with tryptophan24, phenylalanine74, threonine66, threonine68, glutamine76, alanine78, threonine70 and valine85 of the Homer binding domain. The cell-surface receptor of (3) is NMDA receptor or a metabotropic glutamate receptor and the compound stimulates or inhibits the formation of cell surface receptors into clusters.
Preferred Protein: The Homer protein is selected from Homer 1b, 1c, 2a, 2b, 3 or is preferably Homer 1a. The intracellular protein is preferably an inositol triphosphate **receptor**, a **ryanodine receptor**, I42, I30, hInaD or ACK-2. Shank protein is selected from shank 1a, 1b, 3 and cortactin binding protein.
Preferred Compound: The compounds identified are preferably peptides, peptidomimetics, polypeptides, pharmaceuticals, chemical compounds, biological agents, antibodies, neurotropical agents, combinatorial compound libraries or anti-epileptic agents. The peptide of (10) is a cell-surface receptor or an intracellular receptor.
Preferred Cell: The cell is neuronal, glial, cardiac, bronchial, uterine, testicular, liver, renal, intestinal, thymus, spleen. placental, skeletal muscle or a smooth muscle cell.
Preferred Animal: The transgenic animal is a murine.

L4 ANSWER 11 OF 16 WPIDS (C) 2002 THOMSON DERWENT
AN 1999-418858 [35] WPIDS
DNC C1999-123105
TI New 2-(Aryl)-4,7-dioxobenzothiazole derivatives useful as pesticides and **ryanodine receptor** modulators - of defined structures.
DC B02
IN BESCH, H R; BIDASEE, K R; JACKSON, Y A; LYON, M A
PA (ADRE-N) ADVANCED RES & TECHNOLOGY INST; (UYWI-N) UNIV WEST INDIES
CYC 82
PI WO 9932115 A1 19990701 (199935)* EN 38p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW

W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW

AU 9920039 A 19990712 (199950)

ADT WO 9932115 A1 WO 1998-US27002 19981218; AU 9920039 A AU 1999-20039 19981218

FDT AU 9920039 A Based on WO 9932115

PRAI US 1997-71791P 19971219

AB WO 9932115 A UPAB: 19990902

NOVELTY - 2-(Aryl)-4,7-dioxobenzothiazole derivatives (I) useful as pesticides and **ryanodine receptor** modulators are new.

DETAILED DESCRIPTION - Compounds (I), their sugar derivatives and salts are new where:

R2, R3, R4, R5, R6 = Hydrogen (H), electron donating, withdrawing or modulating substituents;

Y5, Y6 = R2, or Y5 + Y6 together are a 4-8 atom carbocyclic, heterocyclic, aromatic or non-aromatic ring optionally substituted with R2

An INDEPENDENT CLAIM is made for compositions comprising (I) and an acceptable carrier.

ACTIVITY - Intracellular **calcium** release modulator; pesticide.

MECHANISM OF ACTION - Selective activator of **ryanodine receptors** associated with intracellular **calcium** release channels. Traditional binding affinity assays on rabbit skeletal muscle sarcoplasmic reticulum membrane vesicles were carried out to compare ryanodine and (A). Using tritium labeled vesicles and liquid scintillation counting, the IC50 values for ryanodine and (A) were 6.2 plus or minus 0.1 and 210 plus or minus 10.8 respectively.

USE - (I) can be used as prophylactic pesticides, **ryanodine receptor** modulators, reagents to alter the intracellular concentrations of **calcium**, or as a treatment to humans for disorders associated with inappropriate intracellular **calcium** levels such as congestive heart failure, migraine, hypertension, premature abortions, Parkinson's disease and Alzheimer's disease.

ADVANTAGE - (I) have a very high affinity for the receptor binding sites. They are more toxic to insects and less toxic to mammals compared to their naturally occurring analogues. They are also easier to make in the laboratory and so offer a cheaper source of **ryanodine receptor** modulator supply.

DESCRIPTION OF DRAWING(S) - Fig 1 shows the reaction scheme for the synthesis of (I).

Dwg.1/1

TECH UPTX: 19990902

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Composition: comprises (I) and a diluent that enhances uptake such as cyclohexadrin, an encapsulating agent.

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: (I) are made following the conventional syntheses illustrated in Fig.1.

L4 ANSWER 12 OF 16 WPIDS (C) 2002 THOMSON DERWENT

AN 1999-204638 [17] WPIDS

DNC C1999-059552

TI Sulphonamide derivatives.

DC B05

IN MCCAFFREY, P; MULLICAN, M D; NOVAK, P M; MULLICAN, M

PA (VERT-N) VERTEX PHARM INC

CYC 84

PI WO 9910340 A1 19990304 (199917)* EN 90p

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZW

ZA 9807478 A 19990428 (199922) 85p
AU 9889236 A 19990316 (199930)
NO 2000000953 A 20000502 (200032)
EP 1007521 A1 20000614 (200033) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
BR 9811923 A 20000815 (200045)
CN 1271354 A 20001025 (200104)
US 6268384 B1 20010731 (200146)
MX 2000002100 A1 20001001 (200158)
KR 2001023413 A 20010326 (200161)
JP 2001514177 W 20010911 (200167) 90p
US 2002013351 A1 20020131 (200210)

ADT WO 9910340 A1 WO 1998-US17816 19980827; ZA 9807478 A ZA 1998-7478 19980819; AU 9889236 A AU 1998-89236 19980827; NO 2000000953 A WO 1998-US17816 19980827, NO 2000-953 20000225; EP 1007521 A1 EP 1998-941093 19980827, WO 1998-US17816 19980827; BR 9811923 A BR 1998-11923 19980827, WO 1998-US17816 19980827; CN 1271354 A CN 1998-809355 19980827; US 6268384 B1 CIP of US 1997-920838 19970829, US 1998-85441 19980527; MX 2000002100 A1 MX 2000-2100 20000229; KR 2001023413 A KR 2000-702055 20000228; JP 2001514177 W WO 1998-US17816 19980827, JP 2000-507669 19980827; US 2002013351 A1 CIP of US 1997-920838 19970829, Div ex US 1998-85441 19980527, US 2001-815193 20010627

FDT AU 9889236 A Based on WO 9910340; EP 1007521 A1 Based on WO 9910340; BR 9811923 A Based on WO 9910340; JP 2001514177 W Based on WO 9910340; US 2002013351 A1 Div ex US 6268384

PRAI US 1998-85441 19980527; US 1997-920838 19970829; US 2001-815193 20010627

AB WO 9910340 A UPAB: 19990511
NOVELTY Sulphonamide derivatives of formula (I) are new. DEFINITIONS H, Ar, 1-6C alkyl (optionally substituted by 5-7C cycloalkyl, 5-7C cycloalkenyl or Ar), 2-6C alkenyl (optionally substituted by 5-7C cycloalkyl, 5-7C cycloalkenyl or Ar) or 2-6C alkynyl (optionally substituted by 5-7C cycloalkyl, 5-7C cycloalkenyl or Ar) in which any methylene is optionally replaced by O, S, SO, SO2 or NR; R=H, 1-6C alkyl, 2-6C alkenyl or 2-6C alkynyl;

Ar=phenyl, 1-naphthyl, 2-naphthyl, indenyl, azulenyl, fluorenyl, anthracenyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, 2-pyrazolinyl, pyrazolidinyl, isoxazolyl, isothiazolyl, 1,2,3-oxadiazolyl, 1,2,3-triazolyl, 1,3,4-thiadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-triazolyl, 1,2,4-oxadiazolyl, 1,2,4-thiadiazolyl, benzoxazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,3,5-triazinyl, 1,3,5-trithianyl, indolizinyl, indolyl, isoindolyl, 3H-indolyl, indolinyl, benzo[b]furanyl, benzo[b]thiophenyl, 1H-indazolyl, benzimidazolyl, benzthiazolyl, purinyl, 4H-quinolizinyl, quinolinyl, 1,2,3,4-tetrahydro-quinolinyl, isoquinolinyl, 1,2,3,4-tetrahydro-isoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, 1,8-naphthyridinyl, pyridinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl or phenoxazinyl, or other mono-, bi- or tri-cyclic 5- to 7-membered rings containing up to 3 heteroatoms (N, NR, O, S, SO or SO2) in which each Ar is optionally substituted by up to 3 of halo, OH, NO2, SO3H, CF3, CF3O, 1-6C alkyl, 2-6C alkenyl, 1-6C alkyloxy, 2-6C alkenyloxy, benzyloxy, phenyloxy, 1,2-methylenedioxy, NR1 R2, carboxyl, N-(1-5C alkyl)carboxamide, N-(2-5C alkenyl)carboxamide,

N,N-di(1-5C alkyl)carboxamide, N,N-di(2-5C alkenyl)carboxamide, N-(1-5C alkyl)sulphonamide, N-(2-5C alkenyl)sulphonamide, N,N-di(1-5C alkyl)sulphonamide, N,N-di(2-5C alkenyl)sulphonamide, morpholinyl, piperidinyl, OZ, CH2(CH2)qZ, O(CH2)qZ, (CH2)q-Z-O-Z or CH=CH-Z; R1, R2 = 1-6C alkyl, 2-6C alkenyl, 2-6C alkynyl, H or benzyl or R1-N-R2 = 5- to 7-membered heterocyclic ring; Z= 4-methoxyphenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrazyl, quinolyl, 3,5-dimethylisoxazoyl, isoxazoyl, 2-methylthiazoyl, thiazoyl, 2-thienyl, 3-thienyl or pyrimidyl;q = 0 to 2; X= N, O or CR; Y= H, Ar, 1-6C alkyl (optionally substituted by 5-7C cycloalkyl, 5-7C cycloalkenyl or Ar), 2-6C alkenyl(optionally substituted by 5-7C cycloalkyl, 5-7C cycloalkenyl or Ar) or 2-6C alkynyl(optionally substituted by 5-7C cycloalkyl, 5-7C cycloalkenyl or Ar); K = 1-6C alkyl (optionally substituted by Ar), 2-6C alkenyl (optionally substituted by Ar), 2-6C alkynyl (optionally substituted by Ar) or cyclohexylmethyl in which any methylene in the alkyl, alkenyl or alkynyl is optionally replaced by O, S, SO, SO2 or NR;n = 0 to 2; J = H, 1-6C alkyl (optionally substituted by Ar), 2-6C alkenyl (optionally substituted by Ar), 2-6C alkynyl (optionally substituted by Ar) or cyclohexylmethyl; D = Ar, 1-6C alkyl (optionally substituted by 5-7C cycloalkyl, 5-7C cycloalkenyl or Ar), 2-6C alkenyl (optionally substituted by 5-7C cycloalkyl, 5-7C cycloalkenyl or Ar), 2-6C alkynyl (optionally substituted by 5-7C cycloalkyl, 5-7C cycloalkenyl or Ar) in which any of the methylene groups in the alkyl chain, other than the one bound to SO2, is optionally replaced by O, S, So, SO2 or NR. INDEPENDENT CLAIMS are included for (i) compounds of formula (II), (III) and (IV); (ii) compounds characterised by (a) possessing neuronal activity, (b) having the ability to increase cytoplasmic **Ca2+** concentration or bind to the **ryanodine receptor**, (c) not binding to FKBP and (d) not possessing MDR reversal activity; (iii) a composition comprising a neurotrophic amount of (I), (II), (III) or (IV) and a carrier. (II) m = 0 to 2; m+n = 1 to 3; ring = optionally unsaturated and up to 2 C-atoms are optionally replaced by O, S, SO, SO2 or NR and is optionally benzofused. (III) R3 = 1-6C alkyl (optionally substituted by Ar), 2-6C alkenyl (optionally substituted by Ar) or 2-6C alkynyl (optionally substituted by Ar) in which any methylene is optionally replaced by O, S, SO, SO2 or NR and in which any methylene except the methylene bound to N is optionally replaced by CO. (IV) when n = 0 and m = 1 then the second methylene of the chain of R3 is not replaced by CO. Preferred Definitions: A, B = one is 1-6C alkyl terminally substituted by pyridyl;X = N or O;J = 1-3C alkyl;K = 1-3C alkyl substituted by phenyl;D = aminophenyl, nitrophenyl, isopropyl, benzyl, fluorophenyl, cyanophenyl, methoxyphenyl, dimethoxyphenyl, methylsulphonylmethyl, ethylenephenyl, dinitroanilinophenyl, N,N-dimethylaminophenylazophenyl, N,N-dimethylaminonaphthyl or acetamidophenyl; Y = methyl;n = 0; m = 2. ORGANIC CHEMISTRY Preparation: e.g. Preferred Composition: The composition may also include a neutrotrophic factor, especially nerve growth factor, insulin growth factor, acidic fibroblast growth factor, basic fibroblast growth factor, platelet-derived growth factor, brain-derived neurotrophic factor, ciliary neurotrophic factor, glial cell-derived neurotrophic factor, neurotrophin-3 or neurotrophin 4/5. ACTIVITY Nerve growth stimulant. MECHANISM OF ACTION (I), (II), (III) and (IV) increase cytoplasmic **Ca2+** concentrations. ADMINISTRATION 0.01 to 10mg/kg/day, preferably 0.1 to 10mg/kg/day. SPECIFIC COMPOUNDS 13 Compounds (III) and (IV) are claimed, e.g. piperidine-2-carboxylic acid benzyl ester. USE (I), (II), (III) and (IV) are useful for stimulating neuronal activity in patients suffering from trigeminal neuralgia, glossopharyngeal neuralgia, Bell's Palsy, myasthenia gravis, muscular dystrophy, muscle injury, progressive muscular atrophy, progressive bulbar inherited muscular dystrophy, herniated, ruptured or prolapsed invertebrae disk syndrome, cervical spondylosis, plexus disorders, thoracic outlet destruction

syndrome, peripheral neuropathies, peripheral myelin disorders, Alzheimer's disease, Gullain-Barre syndrome, Parkinson's disease, ALS, multiple sclerosis, central myelin disorders, stroke, ischemia associated with stroke, neural paropathy, motor neuone disease, sciatic crush, neuropathy associated with diabetes, spinal cord injuries, facial nerve crush, chemotherapy and medication induced neuropathies and Huntington's disease. EXAMPLE A solution of (S)-piperidine-1,2-dicarboxylic acid 1-tert-butyl ester (5g) in CH2Cl2 (50ml) was treated with EDC (6g) and 2-(2-methylaminoethyl)pyridine (3g) for 24 hours. Work up gave 3.8g of (S)-piperidine-1,2-dicarboxylic acid-1-(tert-butyl ester)-2-((N-methyl)-2-pyridinylethyl)amide.A solution of the above compound (3.8g) in CH2Cl2 (25ml) was treated with trifluoroacetic acid (10ml) for 2 hours. Work up gave 2.2g of (2)-piperidine-2-carboxylic acid-2-((n-methyl)-2-pyridylethyl)amide.A solution of the above compound (200mg) in CH2Cl2 (5ml) was treated with Et3N (2ml) and 4-nitrobenzenesulphonyl chloride (260mg) for 24 hours. Work up gave 273mg of N-(4-nitrobenzenesulphonamido)-(S)-piperidine-2-carboxylic acid-2-((N-methyl)-2-pyridylethyl)amide.A solution of the above compound (273mg) in EtOAc (10ml) and EtOH (10ml) was hydrogenated over 10% Pd/C (150mg) for 24 hours. The mixture was filtered and concentrated and the residue was purified by chromatography to give 102mg of N-(4-aminobenzenesulphonamido)-(S)-piperidine-2-carboxylic acid-2-((N-methyl)-2-pyridylethyl)amide.
Dwg.0/0

L4 ANSWER 13 OF 16 WPIDS (C) 2002 THOMSON DERWENT
AN 1996-128595 [13] WPIDS
DNN N1996-108205 DNC C1996-040004
TI New immunogenic ryanodine conjugates for antibody prodn. - and labelled conjugates for identifying **ryanodine receptor** binding site.
DC B02 B04 D16 S03
IN BENTLEY, P; CAMPBELL, K P; KAHL, S D; LEWIS, T; MCPHERSON, P; WINDASS, J D; WITCHER, D R
PA (IOWA) UNIV IOWA STATE RES FOUND INC
CYC 1
PI US 5492839 A 19960220 (199613)* 20p
ADT US 5492839 A US 1994-186435 19940125
PRAI US 1994-186435 19940125
AB US 5492839 A UPAB: 19960329
New immunogenic ryanodine derivs. are cpds. of formula (I) which, when used to immunise an animal, stimulate the prodn. of antibodies which bind specifically to ryanodine with an IC50 below 10-8: Also claimed are: (1) labelled affinity reagents which: (a) bind to the **ryanodine receptor** with an IC50 below 10-8 and are selected from labelled forms of 21-(2-[3,3,3-trifluoro-2-diazo-propionyloxy]-ethylmercapto)-ryanodine (IIa) and 21-(4-hydroxybutylmercapto)-ryanodine (IIb), or (b) bind to the **ryanodine receptor** with an IC50 below 10-7 and are selected from labelled forms of 10-O-(3-[4-azidobenzamido]-propionyl)-ryanodine (IIc), 10-O-(3-[2-nitro-5-azidobenzamido]-propionyl)-ryanodine (IId) and 10-O-(3-[2-benzoylbenzamido]-propionyl)-ryanodine (IIe), and (2) a method for identifying the ryanodine binding site on the **ryanodine receptor**, comprising: (a) providing a labelled affinity reagent which binds to the receptor with an IC50 below 10-7, (b) incubating the reagent with the receptor to form an affinity complex, (c) chemically linking the components of the complex by exposing it to UV light with a wavelength suitable for activating the reagent, (d) digesting the complex to generate peptide fragments and (e) identifying the fragment to which the reagent is linked.
USE - (I) are useful for prodn. of antibodies for use in immunoassays for detecting ryanodine or related cpds., e.g. to screen for cpds. having

ryanodine-like **Ca** channel-modulating activity. Such cpds. could be useful for treating cardiovascular, neuromuscular and neurological disorders or as insecticides. The antibodies could also be used as an antidote to ryanodine intoxication. Information on the **ryanodine receptor** binding site could be useful in designing drugs that mimic the binding characteristics of ryanodine.
Dwg.0/9

L4 ANSWER 14 OF 16 WPIDS (C) 2002 THOMSON DERWENT
AN 1995-254486 [33] WPIDS
CR 1992-382019 [46]; 1996-221316 [22]; 1997-525745 [48]
DNC C1995-116349
TI New ryanodine and dehydro ryanodine derivs. and their labelled derivs. - are used to affect **calcium** ions efflux, isolate **ryanodine receptor** and treat heart disease.
DC B02 K08
IN BESCH, H R; BIDASEE, K R; GERZON, K; HUMERICKHOUSE, R A
PA (INDV) UNIV INDIANA FOUND
CYC 1
PI US 5432288 A 19950711 (199533)* 21p
ADT US 5432288 A CIP of US 1991-687712 19910418, CIP of US 1992-857622 19920325, CIP of US 1993-21349 19930223, US 1993-25150 19930302
PRAI US 1993-25150 19930302; US 1991-687712 19910418; US 1992-857622 19920325; US 1993-21349 19930223
AB US 5432288 A UPAB: 19971209
O10eq.-derivs. of ryanodine and dehydroryanodine of formula (I) are new. In (I), Z is C(H)-CH3 or C=CH2; R is HOOC-CH2CH2-CO- or R1HN(CH2)n-CO; n = 1-3; and R1 is H, Me or a lipophilic gp.

Also new are labelled O10eq. derivs. of ryanodine or dehydroryanodine in which the label, a photo-label, isotopic label or radioactive label, is in the O10 eq. substit.

Also new are cpds. (II) which are cpds. (I) wherein R = R1-NH-C(=N-R1)-NH-(CH2)n-CO and R1 is H or carbobenzyloxy (CBz); and n is 1 or 2.

USE - Cpds. (I) and (II) affect the function of the junctional sarcoplasmic reticulum **Ca2+** release channel of striated muscle. Thus they are potentially useful in the treatment of heart disease esp. as anti-fibrillatory agents. Cpds. (I) and (II) are also useful in affinity chromatography for isolating and purifying the **Ryanodine receptor** and in photo-affinity labelling of the receptor and in preparing anti-ryanodine antibodies using Ryanodine protein-conjugates. Cpds. (II) are also useful intermediates for cpds. (I).
Dwg.0/0

L4 ANSWER 15 OF 16 WPIDS (C) 2002 THOMSON DERWENT
AN 1993-205841 [26] WPIDS
DNN N1993-158328 DNC C1993-091231
TI New DNA from mutant forms of **ryanodine receptor** genes - for detecting susceptibility to malignant hyperthermia.
DC B04 D16 S03
IN BRITT, B A; MACLENNAN, D H; WORTON, R G
PA (HSCR-N) HSC RES & DEV LP; (TORO-N) TORONTO HOSPITAL; (UTOR) UNIV TORONTO INNOVATIONS FOUND
CYC 1
PI CA 2080309 A 19930411 (199326)* 82p
ADT CA 2080309 A CA 1992-2080309 19921009
PRAI GB 1991-21469 19911010
AB **CA 2080309AUPAB**: 19931116
New purified DNA molecule (I) has at least 12 nucleotides from within the sequence of the human RYR1 (skeletal muscle **ryanodine**

receptor) gene having one of the following mutuations: (1) Arg for Gly 248, Cys for Arg 470; Leu for Pro 1785; Cys for Gly 2059, Asn for Lys 2323, His for Arg 2434, Arg for Ala 2839, Arg for Ala 3379, Gly for Glu 4220, (2) a 15 base insertion after G10437 of 5'-GCGGGAGATATACAG and (3) an 18 base deletion between 11572 and 11590, removing Val(3858)-Ile-Asn-Arg-Glu-Asn (3863).

The specification includes the sequence (and derived protein sequence) of most of the RYR7 gene (about 44000 bases).

Ab can be used to detect mutant proteins (e.g. by immunostaining of muscle sections), to determine topology of the receptor at the cell surface, to study structure function relationships, and for immunopptn. or affinity purificn.

The specified mutations have been identified in subjects susceptible to MH.

USE - (I) are useful (1) as probes for screening humans for susceptibiity to malignant hyperthermia (MH), associated with the specified mutuations and (2) as PCR amplificator on primers.

Dwg.0/7

L4 ANSWER 16 OF 16 WPIDS (C) 2002 THOMSON DERWENT
AN 1992-382019 [46] WPIDS
CR 1995-254486 [33]; 1996-221316 [22]; 1997-525745 [48]
DNC C1992-169487
TI Ryania alkaloid O 10 equatorial ester derivs. - useful for opening **calcium** release channels of striated muscle, treating heart disease e.g. fibrillation and receptor isolation.
DC B02
IN BESCH, H R; GERZON, K; HUMERICKHOUSE, R; HUMERICK-HOUSE, R
PA (INDV) UNIV INDIANA FOUND
CYC 36
PI WO 9218499 A1 19921029 (199246)* EN 45p
RW: AT BE CH DE DK ES FR GB GR IT LU MC NL OA SE
W: AU BB BG BR CA CS FI HU JP KP KR LK MG MN MW NO PL RO RU SD US
AU 9218900 A 19921117 (199310)
ADT WO 9218499 A1 WO 1992-US3193 19920417; AU 9218900 A AU 1992-18900 19920417, WO 1992-US3193 19920417
FDT AU 9218900 A Based on WO 9218499
PRAI US 1991-687712 19910418
AB WO 9218499 A UPAB: 19971209

Ryanodine and dehydroryanodine derivs. of formula (I) are new. Z = CH-Me or C=CH2; R = CO(CH2)2CO2H or R1NH(CH2)nCO; n = 1-3; and R1 = H, Me or a lipophilic gp. Isolating and purifying a **ryanodine receptor** comprises attaching (I) to a carrier, passing a fluid mixt. (derived from cardiac or skeletal muscle sarcoplasmic reticulum (SR) and contg. **ryanodine receptor**) over modified carrier and sepg. receptor from carrier. Pref. lipophilic gps. = adamantane, adamantylmethyl adamantyl-1-oxy or benzyloxy carbonyl, adamantoyl-glycyl, phenylacetyl, biotinyl-beta-alanyl, 'BODIPY(Fl-C3)'(RTM), 7-amino-4-methyl coumarinyl-3-acetyl and benzoyl (opt. substd. by eg. halo, 1-4C alkoxy or 1-4C alkyl).

USE - Ryanodine protein conjugates for antibody prepn..

Dwg.0/0

text search


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=> d his

     (FILE 'HCAPLUS' ENTERED AT 08:58:06 ON 04 NOV 2002)
               DEL HIS Y

     FILE 'REGISTRY' ENTERED AT 08:59:48 ON 04 NOV 2002
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               E CALCIUM/CN
L2             1 S E3

     FILE 'HCAPLUS' ENTERED AT 09:01:41 ON 04 NOV 2002
L3           384 S L1
L4        294775 S L2
L5           265 S L3 AND L4
L6            15 S L5 AND MODUL?
L7         28536 S IMMUN? (L) (DISEASE# OR DISORDER?)
L8             1 S L7 AND L5
L9             3 S L5 AND IMMUN?
L10            3 S L9 OR L8
L11          280 S L3 AND (CA OR CALCIUM OR L2)
L12            3 S L11 AND IMMU?
L13            3 S L12 OR L10
L14         2129 S RYANODINE (L) RECEPT?
L15         1705 S L14 AND (L4 OR CA OR CALCIUM)
L16           44 S L15 AND IMMUN?
L17        33142 S (L4 OR CA OR CALCIUM) (L) CHANNEL?
L18           26 S L17 AND L16
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DICTIONARY FILE UPDATES:    3 NOV 2002  HIGHEST RN 469858-87-5

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Experimental and calculated property data are now available.  See HELP
PROPERTIES for more information.  See STNote 27, Searching Properties
in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

=> d que l1;d l1
L1             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  119340-53-3

L1   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2002 ACS
RN   119340-53-3  REGISTRY
CN   Adenosine 5'-(trihydrogen diphosphate), 1-.beta.-D-ribofuranosyl-,
     intramol. P'.fwdarw.5''-ester (9CI)  (CA INDEX NAME)
OTHER NAMES:
CN   cADPR
CN   cADP-ribose
CN   Cyclic ADP-ribose
FS   STEREOSEARCH
DR   143822-66-6, 150155-83-2
MF   C15 H21 N5 O13 P2
CI   COM
SR   CA
LC   STN Files:   AGRICOLA, ANABSTR, BIOBUSINESS, BIOSIS, CA, CANCERLIT,
       CAPLUS, CASREACT, CHEMCATS, CSCHEM, MEDLINE, TOXCENTER, USPATFULL

Absolute stereochemistry.
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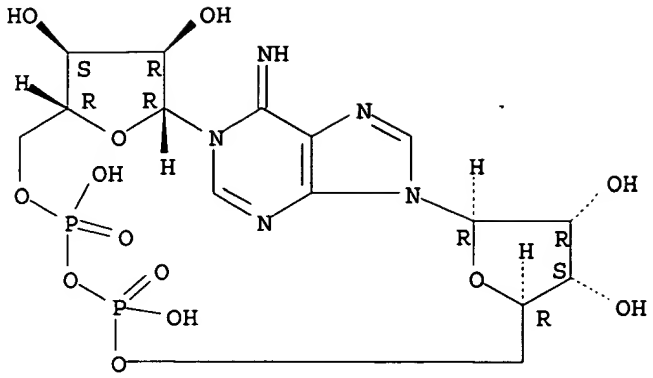

369 REFERENCES IN FILE CA (1962 TO DATE)
6 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
369 REFERENCES IN FILE CAPLUS (1962 TO DATE)

=> d que l2;d l2
L2 1 SEA FILE=REGISTRY ABB=ON PLU=ON CALCIUM/CN

L2 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2002 ACS
RN 7440-70-2 REGISTRY
CN **Calcium (8CI, 9CI)** (CA INDEX NAME)
OTHER NAMES:
CN Atomic calcium
CN Blood-coagulation factor IV
CN Calcium atom
CN Calcium element
CN Praval
DR 8047-59-4
MF Ca
CI COM
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, AQUIRE, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, CSNB, DDFU, DETHERM*, DIOGENES, DIPPR*, DRUGU, EMBASE, ENCOMPLIT, ENCOMPLIT2, ENCOMPPAT, ENCOMPPAT2, HSDB*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS, NAPRALERT, NIOSHTIC, PHARMASEARCH, PIRA, PROMT, TOXCENTER, TULSA, ULIDAT, USPAT2, USPATFULL, VETU, VTB
(*File contains numerically searchable property data)
Other Sources: DSL**, EINECS**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)

Ca

296018 REFERENCES IN FILE CA (1962 TO DATE)
6426 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
296150 REFERENCES IN FILE CAPLUS (1962 TO DATE)
1 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

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FILE LAST UPDATED: 3 Nov 2002  (20021103/ED)

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     (FILE 'HCAPLUS' ENTERED AT 09:01:41 ON 04 NOV 2002)
L3           384 S L1
L4        294775 S L2
L5           265 S L3 AND L4
L6            15 S L5 AND MODUL?
L7         28536 S IMMUN? (L) (DISEASE# OR DISORDER?)
L8             1 S L7 AND L5
L9             3 S L5 AND IMMUN?
L10            3 S L9 OR L8
L11          280 S L3 AND (CA OR CALCIUM OR L2)
L12            3 S L11 AND IMMU?
L13            3 S L12 OR L10
L14         2129 S RYANODINE (L) RECEPT?
L15         1705 S L14 AND (L4 OR CA OR CALCIUM)
L16           44 S L15 AND IMMUN?
L17        33142 S (L4 OR CA OR CALCIUM) (L) CHANNEL?
L18           26 S L17 AND L16

     FILE 'REGISTRY' ENTERED AT 09:09:03 ON 04 NOV 2002

     FILE 'HCAPLUS' ENTERED AT 09:09:15 ON 04 NOV 2002

=> d .ca l6 1-15;d .ca l13 1-3;d .ca l18 1-26

L6   ANSWER 1 OF 15  HCAPLUS  COPYRIGHT 2002 ACS
ACCESSION NUMBER:         2002:696553  HCAPLUS
DOCUMENT NUMBER:          137:231357
TITLE:                    Shistosoma mansoni-derived chemotactic SM38 protein
                          for screening drugs capable of modulating
```

CD38-**modulated** chemotaxis and treating related diseases

INVENTOR(S): Lund, Frances E.; Randall, Troy D.; Partida-Sanchez, Santiago

PATENT ASSIGNEE(S): USA

SOURCE: U.S. Pat. Appl. Publ., 41 pp.
CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002127646	A1	20020912	US 2001-982616	20011017
WO 2002032288	A2	20020425	WO 2001-US32383	20011017
WO 2002032288	A3	20020711		

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RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2000-241065P P 20001017

AB The present invention relates to methods for modulating the migratory activity of cells expressing CD38 for the treatment of disorders including, but not limited to, inflammation, ischemia, asthma, autoimmune disease, diabetes, arthritis, allergies, infection with pathogenic organisms and transplant rejection. Such cells include, for example, neutrophils, lymphocytes, eosinophils, macrophages and dendritic cells. The invention further relates to drug screening assays designed to identify compds. that modulate the ADP-ribosyl cyclase activity of CD38 and the use of such compds. in the treatment of disorders involving CD38 modulated cell migration. The invention is based on the discovery that CD38 ADP-ribosyl cyclase activity is required for chemotaxis. Furthermore, the invention relates to methods for identifying compds. that modulate the enzyme activity of the S. mansoni CD38 homolog and using those compds. in the treatment of pathol. disorders caused by helminth infection. This is based on the discovery that helminths such as S. mansoni express CD38 homologues.

IC ICM G01N033-567
ICS C07H021-04; C12P021-02; C12N005-06; C07K014-705

NCL 435069100

CC 15-2 (Immunochemistry)
Section cross-reference(s): 1, 3, 10

IT Animal cell
(CD38-expressing; Shistosoma mansoni-derived chemotactic SM38 protein for screening drugs capable of **modulating** CD38-**modulated** chemotaxis and treating related diseases)

IT Disease, animal
(CD38-mediated; Shistosoma mansoni-derived chemotactic SM38 protein for screening drugs capable of **modulating** CD38-**modulated** chemotaxis and treating related diseases)

IT Chemotactic factors
RL: ARG (Analytical reagent use); BPN (Biosynthetic preparation); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use);

ANST (Analytical study); BIOL (Biological study); PREP (Preparation); USES (Uses)
(SM38 protein; Shistosoma mansoni-derived chemotactic SM38 protein for screening drugs capable of **modulating** CD38-**modulated** chemotaxis and treating related diseases)

IT Gene, microbial
Proteins
RL: ARG (Analytical reagent use); BPN (Biosynthetic preparation); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); PREP (Preparation); USES (Uses)
(SM38; Shistosoma mansoni-derived chemotactic SM38 protein for screening drugs capable of **modulating** CD38-**modulated** chemotaxis and treating related diseases)

IT Allergy
Arthritis
Asthma
Autoimmune disease
Chemotaxis
DNA sequences
Dendritic cell
Diabetes mellitus
Drug screening
Eosinophil
Infection
Inflammation
Ischemia
Lymphocyte
Macrophage
Molecular cloning
Neutrophil
Parasitic worm
Pathogen
Protein sequences
Schistosoma mansoni
Transplant rejection
(Shistosoma mansoni-derived chemotactic SM38 protein for screening drugs capable of **modulating** CD38-**modulated** chemotaxis and treating related diseases)

IT CD38 (antigen)
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); BIOL (Biological study)
(Shistosoma mansoni-derived chemotactic SM38 protein for screening drugs capable of **modulating** CD38-**modulated** chemotaxis and treating related diseases)

IT Antibodies
Antisense oligonucleotides
Fusion proteins (chimeric proteins)
RL: ARU (Analytical role, unclassified); BSU (Biological study, unclassified); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(Shistosoma mansoni-derived chemotactic SM38 protein for screening drugs capable of **modulating** CD38-**modulated** chemotaxis and treating related diseases)

IT Lung, disease
(allergy; Shistosoma mansoni-derived chemotactic SM38 protein for screening drugs capable of **modulating** CD38-**modulated** chemotaxis and treating related diseases)

IT Cytokine receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)

(chemotactic factor; Shistosoma mansoni-derived chemotactic SM38 protein for screening drugs capable of **modulating** CD38-**modulated** chemotaxis and treating related diseases)

IT Neutrophil
(chemotaxis; Shistosoma mansoni-derived chemotactic SM38 protein for screening drugs capable of **modulating** CD38-**modulated** chemotaxis and treating related diseases)

IT Cell migration
(**modulation**; Shistosoma mansoni-derived chemotactic SM38 protein for screening drugs capable of **modulating** CD38-**modulated** chemotaxis and treating related diseases)

IT Chemotaxis
(neutrophil; Shistosoma mansoni-derived chemotactic SM38 protein for screening drugs capable of **modulating** CD38-**modulated** chemotaxis and treating related diseases)

IT Animal
(transgenic; Shistosoma mansoni-derived chemotactic SM38 protein for screening drugs capable of **modulating** CD38-**modulated** chemotaxis and treating related diseases)

IT 135622-82-1, ADP-ribosyl cyclase
RL: ARU (Analytical role, unclassified); BSU (Biological study, unclassified); ANST (Analytical study); BIOL (Biological study)
(CD38; Shistosoma mansoni-derived chemotactic SM38 protein for screening drugs capable of **modulating** CD38-**modulated** chemotaxis and treating related diseases)

IT 5502-96-5, Nicotinic acid adenine dinucleotide phosphate
119340-53-3, CADPR
RL: ANT (Analyte); BSU (Biological study, unclassified); ANST (Analytical study); BIOL (Biological study)
(Shistosoma mansoni-derived chemotactic SM38 protein for screening drugs capable of **modulating** CD38-**modulated** chemotaxis and treating related diseases)

IT 458574-83-9P
RL: ARG (Analytical reagent use); BPN (Biosynthetic preparation); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); PREP (Preparation); USES (Uses)
(amino acid sequence; Shistosoma mansoni-derived chemotactic SM38 protein for screening drugs capable of **modulating** CD38-**modulated** chemotaxis and treating related diseases)

IT **7440-70-2**, Calcium, biological studies
RL: ANT (Analyte); BSU (Biological study, unclassified); ANST (Analytical study); BIOL (Biological study)
(intracellular; Shistosoma mansoni-derived chemotactic SM38 protein for screening drugs capable of **modulating** CD38-**modulated** chemotaxis and treating related diseases)

IT 458574-82-8P
RL: ARG (Analytical reagent use); BPN (Biosynthetic preparation); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); PREP (Preparation); USES (Uses)
(nucleotide sequence; Shistosoma mansoni-derived chemotactic SM38 protein for screening drugs capable of **modulating** CD38-**modulated** chemotaxis and treating related diseases)

IT 458619-61-9 458619-62-0 458619-63-1 458619-64-2 458619-65-3 458619-66-4 458619-67-5 458619-68-6 458619-69-7 458619-70-0 458619-71-1 458619-72-2 458619-73-3
RL: PRP (Properties)
(unclaimed sequence; shistosoma mansoni-derived chemotactic SM38 protein for screening drugs capable of **modulating** CD38-

modulated chemotaxis and treating related diseases)

L6 ANSWER 2 OF 15 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:122798 HCAPLUS
DOCUMENT NUMBER: 136:177974
TITLE: Nicotinic acid adenine dinucleotide phosphate (NAADP) analogs for **modulating** T-cell activity
INVENTOR(S): Potter, Barry V. L.; Guse, Andreas H.; Mayr, Georg W.; Berg, Ingeborg
PATENT ASSIGNEE(S): University of Bath, UK
SOURCE: PCT Int. Appl., 83 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002011736	A1	20020214	WO 2001-GB3440	20010731
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2001075732	A5	20020218	AU 2001-75732	20010731

PRIORITY APPLN. INFO.: GB 2000-19234 A 20000804
WO 2001-GB3440 W 20010731
OTHER SOURCE(S): MARPAT 136:177974
AB A method for modulating T cell activity by modulating the intracellular concn. and/or activity of NAADP+, compds. capable of modulating the effect of NAADP+ on T cell Ca+2 levels, and methods for identifying such compds., are described. Prepn. of 8-bromo-nicotinic acid adenine dinucleotide phosphate is described.
IC ICM A61K031-70
ICS C07H021-02; C07H019-207
CC 1-7 (Pharmacology)
Section cross-reference(s): 33
IT Addison's disease
Antirheumatic agents
Autoimmune disease
Drug screening
Hepatitis
Immunomodulators
Lupus erythematosus
Myasthenia gravis
Signal transduction, biological
T cell (lymphocyte)
Transplant rejection
(NAADP analogs for **modulating** T-cell activity)
IT TCR (T cell receptors)
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(NAADP analogs for **modulating** T-cell activity)
IT Cell proliferation
(T cell; NAADP analogs for **modulating** T-cell activity)
IT Cell differentiation

Cytotoxic agents
(T-cell; NAADP analogs for **modulating** T-cell activity)
IT Immune tolerance
(anergy, T-cell; NAADP analogs for **modulating** T-cell activity)
IT CD3 (antigen)
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(complexes, with TCR; NAADP analogs for **modulating** T-cell activity)
IT Immunity
(disorder; NAADP analogs for **modulating** T-cell activity)
IT Pancreatic islet of Langerhans
(insulitis; NAADP analogs for **modulating** T-cell activity)
IT Eye, disease
(iridocyclitis; NAADP analogs for **modulating** T-cell activity)
IT Testis, disease
(orchitis; NAADP analogs for **modulating** T-cell activity)
IT T cell (lymphocyte)
(proliferation; NAADP analogs for **modulating** T-cell activity)
IT Multiple sclerosis
(therapeutic agents; NAADP analogs for **modulating** T-cell activity)
IT Thyroid gland, disease
(thyroiditis; NAADP analogs for **modulating** T-cell activity)
IT Eye, disease
(uveitis; NAADP analogs for **modulating** T-cell activity)
IT 5502-96-5, Nicotinic acid adenine dinucleotide phosphate **7440-70-2**, Calcium, biological studies 88269-39-0, Inositol-1,4,5-trisphosphate **119340-53-3**, CADPR
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(NAADP analogs for **modulating** T-cell activity)
IT 9032-65-9, NADase
RL: CAT (Catalyst use); USES (Uses)
(NAADP analogs for **modulating** T-cell activity)
IT 113596-09-1 398460-86-1
RL: PAC (Pharmacological activity); BIOL (Biological study)
(NAADP analogs for **modulating** T-cell activity)
IT 62828-70-0P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(NAADP analogs for **modulating** T-cell activity)
IT 5502-96-5D, Nicotinic acid adenine dinucleotide phosphate, analogs
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(NAADP analogs for **modulating** T-cell activity)
IT 53-59-8P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. and reaction; NAADP analogs for **modulating** T-cell activity)
IT 59-67-6, Nicotinic acid, reactions 24292-60-2
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction; NAADP analogs for **modulating** T-cell activity)
REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 3 OF 15 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:812031 HCAPLUS
DOCUMENT NUMBER: 136:128997

TITLE: Pharmacological characterization of the putative cADP-ribose receptor
AUTHOR(S): Thomas, Justyn M.; Masgrau, Roser; Churchill, Grant C.; Galione, Antony
CORPORATE SOURCE: Department of Pharmacology, University of Oxford, Oxford, OX1 3QT, UK
SOURCE: Biochemical Journal (2001), 359(2), 451-457
CODEN: BIJOAK; ISSN: 0264-6021
PUBLISHER: Portland Press Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB CADP-ribose (cADPR), a naturally occurring metabolite of NAD+, has been shown to be an important regulator of intracellular Ca2+ release. Considerable evidence suggests that cADPR is the endogenous modulator of the ryanodine receptor (RyR), which mediates Ca2+-induced Ca2+ release (CICR). Indeed, cADPR-mediated Ca2+ release is subject to functional regulation by other modulators of CICR, including Ca2+, caffeine and calmodulin. However, the underlying basis behind the effect of such agents on cADPR activity (in particular whether they regulate cADPR binding), as well as the precise nature of the cADPR receptor remains unclear. In the present study, use of 32P-radiolabeled cADPR has enabled a detailed pharmacol. characterization of cADPR-binding sites in sea urchin egg homogenates. We report that cADPR binds specifically to a single class of high affinity receptor. Retainment of binding to membranes after a high-salt wash suggests the involvement of either an integral membrane protein (possibly the RyR itself) or a peripheral protein tightly assocd. to the membrane. Insensitivity of [32P]cADPR binding to either FK506 or rapamycin suggests that this does not concern the FK506-binding protein. Significantly, binding is highly robust, being relatively insensitive to both endogenous and pharmacol. modulators of RyR-mediated CICR. In turn, this suggests that such agents modulate cADPR-mediated Ca2+ release primarily by tuning the "gain" of the CICR system, upon which cADPR acts, rather than influencing the interaction of cADPR with its target receptor. The exception to this is calmodulin, for which our results indicate an addnl. role in facilitating cADPR binding.

CC 1-12 (Pharmacology)

IT Biological transport
(calcium; pharmacol. characterization of putative cADP-ribose receptor in relation to functional **modulation** of cADPR by ryanodine receptor/Ca2+-induced Ca2+ release **modulators**)

IT Receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(pharmacol. characterization of putative cADP-ribose receptor in relation to functional **modulation** of cADPR by ryanodine receptor/Ca2+-induced Ca2+ release **modulators**)

IT Calmodulins
RL: PAC (Pharmacological activity); BIOL (Biological study)
(pharmacol. characterization of putative cADP-ribose receptor in relation to functional **modulation** of cADPR by ryanodine receptor/Ca2+-induced Ca2+ release **modulators**)

IT **119340-53-3**, Cyclic ADP-ribose
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(pharmacol. characterization of putative cADP-ribose receptor in relation to functional **modulation** of cADPR by ryanodine receptor/Ca2+-induced Ca2+ release **modulators**)

IT 58-08-2, Caffeine, biological studies 94-24-6, Tetracaine 11103-72-3, Ruthenium red 53123-88-9, Rapamycin 104987-11-3, FK506
RL: PAC (Pharmacological activity); BIOL (Biological study)
(pharmacol. characterization of putative cADP-ribose receptor in relation to functional **modulation** of cADPR by ryanodine

receptor/Ca2+-induced Ca2+ release **modulators**)
IT **7440-70-2**, Calcium, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(transport; pharmacol. characterization of putative cADP-ribose receptor in relation to functional **modulation** of cADPR by ryanodine receptor/Ca2+-induced Ca2+ release **modulators**)
REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 4 OF 15 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:759350 HCAPLUS
DOCUMENT NUMBER: 136:64388
TITLE: Spontaneous transient outward currents: **modulation** by nociceptin in murine dentate gyrus granule cells
AUTHOR(S): Shirasaki, Tetsuya; Houtani, Takeshi; Sugimoto, Tetsuo; Matsuda, Hiroko
CORPORATE SOURCE: Department of Physiology, Kansai Medical University, Osaka, Moriguchi, 570-8506, Japan
SOURCE: Brain Research (2001), 917(2), 191-205
CODEN: BRREAP; ISSN: 0006-8993
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Spontaneous transient outward currents have been found in peripheral neurons and smooth muscle cells, but rarely in central neurons. Using a nystatin-perforated patch clamp technique, we succeeded in recording spontaneous transient outward currents in mouse dentate gyrus granule cells. Nociceptin/orphanin FQ increased the amplitude and frequency of transient outward currents. We consider modulation of spontaneous transient outward currents to be a new means to regulate cell activity in central neurons, and studied their characteristics and mechanism of augmentation. The whole-cell current-voltage relationship showed outward rectification and the reversal potential was close to the equil. potential for K+. The frequency of spontaneous transient outward currents increased at depolarized potentials. Tetraethylammonium, iberiotoxin and a Ca2+ chelator BAPTA-AM inhibited spontaneous transient outward currents. These results suggest the involvement of large-conductance Ca2+-activated K+ channels. Single-channel recordings in the inside-out configuration revealed Ca2+-activated K+ channels with a conductance ranging from 82 to 352 pS. The augmenting effect of nociceptin/orphanin FQ was cancelled by [Phe1.psi.(CH2-NH)Gly2]Nociceptin(1-13)NH2. Cd2+ did not affect the transient outward currents or augmentation by nociceptin/orphanin FQ. Whereas nociceptin/orphanin FQ, theophylline and cyclic ADP ribose induced transient outward currents with short duration obsd. under control conditions, inositol 1,4,5-trisphosphate induced transient outward currents with long duration, in addn. to those with short duration. Ryanodine inhibited nociceptin/orphanin FQ from augmenting spontaneous transient outward currents. Our data suggest that Ca2+ sparks transiently activate large-conductance Ca2+-activated K+ channels to induce transient outward currents. Nociceptin/orphanin FQ probably sensitizes ryanodine receptors and increases transient outward currents to reduce cell excitability.
CC 2-5 (Mammalian Hormones)
IT Brain
(dentate gyrus, granule cell layer; nociceptin **modulation** of spontaneous transient outward currents in murine dentate gyrus granule cells and mechanism thereof)
IT Neurotransmission
(nociceptin **modulation** of spontaneous transient outward

currents in murine dentate gyrus granule cells and mechanism thereof)
IT Potassium channel
Ryanodine receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(nociceptin **modulation** of spontaneous transient outward currents in murine dentate gyrus granule cells and mechanism thereof)
IT Biological transport
(potassium; nociceptin **modulation** of spontaneous transient outward currents in murine dentate gyrus granule cells and mechanism thereof)
IT 58-55-9, Theophylline, biological studies 7440-09-7, Potassium, biological studies **7440-70-2**, Calcium, biological studies 88269-39-0, Inositol 1,4,5-trisphosphate **119340-53-3**, Cyclic ADP ribose 170713-75-4, Nociceptin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(nociceptin **modulation** of spontaneous transient outward currents in murine dentate gyrus granule cells and mechanism thereof)
REFERENCE COUNT: 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 5 OF 15 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:393421 HCAPLUS
DOCUMENT NUMBER: 133:117995
TITLE: Ca2+-induced Ca2+ release supports the relay mode of activity in thalamocortical cells
AUTHOR(S): Budde, Thomas; Sieg, Frank; Braunewell, Karl-Heinz; Gundelfinger, Eckart D.; Pape, Hans-Christian
CORPORATE SOURCE: Institut fur Physiologie Otto-von-Guericke-Universitat, Magdeburg, D-39120, Germany
SOURCE: Neuron (2000), 26(2), 483-492
CODEN: NERNET; ISSN: 0896-6273
PUBLISHER: Cell Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Ca2+ ions play an important role during rhythmic bursting of thalamocortical neurons within sleep. The function of Ca2+ during the tonic relay mode of these neurons during wakefulness is less clear. Here, we report that tonic activity in thalamocortical cells results in an increase in the intracellular Ca2+ concn. and subsequent release of Ca2+ from intracellular stores mediated via ryanodine receptors (RyRs). Blockade of Ca2+ release shifted the regular firing of single action potentials toward the generation of spike clusters. Regular spike firing and intracellular Ca2+ release thus appear to be functionally coupled in a pos. feedback manner, thereby supporting the relay mode of thalamocortical cells during wakefulness. Regulatory influences may be coupled to this system via the cyclic ADP ribose pathway.
CC 13-6 (Mammalian Biochemistry)
IT **119340-53-3**, Cyclic ADP ribose
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(**modulation** by cyclic ADP ribose of Ca2+-induced Ca2+ release mediated via ryanodine receptors during relay mode of activity of thalamocortical cells during wakefulness)
IT **7440-70-2**, Calcium, biological studies
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(transport; Ca2+-induced Ca2+ release mediated via ryanodine receptors during relay mode of activity of thalamocortical cells during wakefulness)

REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 6 OF 15 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:373917 HCAPLUS
DOCUMENT NUMBER: 133:100971
TITLE: Novel mechanisms involved in superoxide anion radical-triggered Ca2+ release from cardiac sarcoplasmic reticulum linked to cyclic ADP-ribose stimulation
AUTHOR(S): Kumasaka, Satoru; Shoji, Hirofumi; Okabe, Eiichiro
CORPORATE SOURCE: Department of Pharmacology and ESR Laboratory, Kanagawa Dental College, Kanagawa, 238-0003, Japan
SOURCE: Antioxidants & Redox Signaling (1999), 1(1), 55-69
CODEN: ARSIF2; ISSN: 1523-0864
PUBLISHER: Mary Ann Liebert
DOCUMENT TYPE: Journal
LANGUAGE: English

AB It has been suggested that cyclic adenosine 5'-diphosphoribose (cADPR) directly activates the cardiac isoform of the ryanodine receptor (RyR)/Ca2+ release channel. We have previously shown that selective activation of RyR/Ca2+ release channel by superoxide anion radical (O2.cntdot.-) is dependent of the presence of calmodulin and identified calmodulin as a functional mediator of O2.cntdot.--triggered Ca2+ release through the RyR/Ca2+ release channel of cardiac sarcoplasmic reticulum (SR). We now demonstrate that although the effect of O2.cntdot.- on Ca2+ efflux from RyR/Ca2+ release channel at higher concns. (>5 .mu.M) is due to its ability to produce a loss in function of calmodulin thereby decreasing calmodulin inhibition, O2.cntdot.- radicals at lower concns. (<5 .mu.M) may be able to stimulate Ca2+ release only in the presence of calmodulin from the SR via increased cADPR synthesis; it is also shown that cADPR is a modulator that can activate the Ca2+-release mechanism when it is in a sensitized state by the presence of calmodulin, possibly, at physiol. concn. In addn., the SR vesicles immediately upon addn. of cADPR, but not NAD+, did exhibit Ca2+ efflux stimulation. When heart homogenate was incubated with O2.cntdot.-, conversion of NAD+ into cADPR was stimulated; the redn. of homogenate Ca2+ uptake (by increasing Ca2+ efflux through RyR/Ca2+ release channel) occurred. Thus O2.cntdot.- radical is responsible for cADPR formation from NAD+ in the cellular environment outside of the SR of heart muscle. The results presented here provide the first evidence of a messenger role for O2.cntdot.- radical in cADPR-mediated Ca2+ mobilization in myocardium.

CC 6-1 (General Biochemistry)
Section cross-reference(s): 13

IT Calmodulins
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(in **modulating** effect of superoxide anion; novel mechanisms involved in superoxide anion radical-triggered Ca2+ release from cardiac sarcoplasmic reticulum linked to cyclic ADP-ribose stimulation)

IT **119340-53-3**, Cyclic ADP-ribose
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(novel mechanisms involved in superoxide anion radical-triggered Ca2+ release from RyR/Ca2+ release channel of cardiac sarcoplasmic reticulum linked to cyclic ADP-ribose stimulation and conversion of NAD+ into cADPR)

IT **7440-70-2**, Calcium, biological studies

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(transport; novel mechanisms involved in superoxide anion radical-triggered Ca2+ release from cardiac sarcoplasmic reticulum linked to cyclic ADP-ribose stimulation)
REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 7 OF 15 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:199123 HCAPLUS
DOCUMENT NUMBER: 131:1765
TITLE: Cyclic ADP-ribose-dependent Ca2+ release is **modulated** by free [Ca2+] in the scallop sarcoplasmic reticulum
AUTHOR(S): Panfoli, Isabella; Burlando, Bruno; Viarengo, Aldo
CORPORATE SOURCE: Istituto Policattedra di Chimica Biologica, Universita di Genova, Genoa, 16132, Italy
SOURCE: Biochemical and Biophysical Research Communications (1999), 257(1), 57-62
CODEN: BBRCA9; ISSN: 0006-291X
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Cyclic ADP-ribose (cADPR) elicits calcium-induced calcium release (CICR) in a variety of cell types. We studied the effect of cADPR on Ca2+ release in muscle cells by incubating SR vesicles from scallop (Pecten jacobaeus) adductor muscle in the presence of the Ca2+ tracer fluo-3. Exposure of SR to cADPR (20 .mu.M) produced Ca2+ release, which was a function of free [Ca2+] in a range between .apprx.150 and 1000 nM, indicating an involvement of ryanodine-sensitive Ca2+ channels. This Ca2+ release was not significantly enhanced by calmodulin (7 .mu.g/mL), but it was enhanced by equimolar addn. of noncyclic ADPR. Also, the Ca2+ release elicited by cADPR/ADPR was a function of free [Ca2+] in a range between .apprx.150 and 3000 nM, over which Ca2+ was inhibitory. CADPR self-inactivation was obsd. at low free [Ca] (.apprx.150 nM), but it tended to disappear upon [Ca] elevation (.apprx.250 nM). Caffeine or ryanodine induced a Ca2+ release which was ruthenium red (2.5 .mu.M) sensitive at low [Ca2+]. However, the Ca2+ release induced by either ryanodine or cADPR was no longer ruthenium red sensitive when free [Ca2+] was increased. Based on these data, a model is proposed for Ca2+ signaling in muscle cells, where a steady-state cADPR level would trigger Ca2+ release when free [Ca2+] does reach a threshold slightly above its resting level, hence producing cascade RyR recruitment along SR cisternae from initial Ca2+ signaling sites. (c) 1999 Academic Press.
CC 6-1 (General Biochemistry)
Section cross-reference(s): 12
IT Muscle
(adductor; cyclic ADP-ribose-dependent calcium release is **modulated** by free calcium in scallop muscle sarcoplasmic reticulum)
IT Biological transport
(calcium; cyclic ADP-ribose-dependent calcium release is **modulated** by free calcium in scallop muscle sarcoplasmic reticulum)
IT Pecten jacobaeus
Signal transduction, biological
Simulation and Modeling, biological
(cyclic ADP-ribose-dependent calcium release is **modulated** by free calcium in scallop muscle sarcoplasmic reticulum)
IT Calcium channel

Ryanodine receptors
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(cyclic ADP-ribose-dependent calcium release is **modulated** by free calcium in scallop muscle sarcoplasmic reticulum)

IT Biological transport
(intracellular; cyclic ADP-ribose-dependent calcium release is **modulated** by free calcium in scallop muscle sarcoplasmic reticulum)

IT Endoplasmic reticulum
(sarcoplasmic reticulum; cyclic ADP-ribose-dependent calcium release is **modulated** by free calcium in scallop muscle sarcoplasmic reticulum)

IT 135622-82-1, ADP-Ribosyl cyclase
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(cyclic ADP-ribose-dependent calcium release is **modulated** by free calcium in scallop muscle sarcoplasmic reticulum)

IT 20762-30-5, ADP-Ribose **119340-53-3**, Cyclic ADP-Ribose
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(cyclic ADP-ribose-dependent calcium release is **modulated** by free calcium in scallop muscle sarcoplasmic reticulum)

IT **7440-70-2**, Calcium, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(cyclic ADP-ribose-dependent calcium release is **modulated** by free calcium in scallop muscle sarcoplasmic reticulum)

IT **7440-70-2**, Calcium, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(transport; cyclic ADP-ribose-dependent calcium release is **modulated** by free calcium in scallop muscle sarcoplasmic reticulum)

REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 8 OF 15 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:416110 HCAPLUS
DOCUMENT NUMBER: 127:78980
TITLE: **Modulator** and messenger functions of cyclic ADP-ribose in calcium signaling
AUTHOR(S): Lee, Hon Cheung
CORPORATE SOURCE: Department of Physiology, University of Minnesota, Minneapolis, MN, 55455, USA
SOURCE: Recent Progress in Hormone Research (1996), Volume Date 1995, 51, 355-389
CODEN: RPHRA6; ISSN: 0079-9963
PUBLISHER: Endocrine Society
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review, with 86 refs. Cyclic ADP-ribose (cADPR), a Ca+2 mobilizing cyclic nucleotide derived from NAD+, is emerging as an endogenous modulator of the Ca+2-induced Ca+2 release (CICR) mechanism in cells. CADPR was discovered because of the prominent delay in the initiation of Ca+2 release by NAD+ in sea urchin egg homogenates, which was due to enzymic conversion to cADPR. In addn. to the egg, an invertebrate cell, amphibian neurons, a variety of mammalian cells and plant vacuoles are

found to be responsive to cADPR, indicating its generality. The cyclic structure of cADPR has been detd. by x-ray crystallog. A series of analogs has been synthesized, which includes cyclic GDP-ribose, a fluorescent analog, a series of specific antagonists, a photoaffinity label and caged cADPR. The use of these analogs of cADPR has provided definitive evidence for the authenticity of its Ca+2 mobilizing activity and insights for understanding its mechanisms and biol. functions. Show that its action requires a sol. protein which is identified as calmodulin. The effect of calmodulin is synergistic with cADPR and both act to sensitize CICR to Ca+2. Together, the Ca+2 sensitivity of CICR can be increased by several orders of magnitude. In addn. to being a modulator of CICR, cADPR can also function as a messenger. Activation of its synthetic enzyme can lead to large increases in cellular concns. of cADPR, which would sensitize CICR to such an extent that even basal levels of cellular Ca+2 are sufficient to trigger further release. This is operationally equiv. to being a Ca+2 messenger. Three types of enzymes are involved in the metab. of cADPR, a sol. ADP-ribosyl cyclase; a bifunctional ecto-enzyme, CD38, which is also a lymphocyte antigen; and an intracellular enzyme activable by a cGMP-dependent process. The importance of two cysteine residues in the bifunctionality of CD38 has been shown by site-directed mutagenesis. Both ADP-ribosyl cyclase and CD38 can catalyze the exchange of the nicotinamide group in NADP+ with nicotinic acid, leading to the formation of another Ca+2 mobilizing metabolite, nicotinic acid dinucleotide phosphate (NAADP). Pharmacol. and desensitization studies show that the NAADP-mechanism is totally independent of the cADPR- and inositol trisphosphate-mechanisms and the Ca+2 stores responsive to NAADP are separable from those sensitive to the other two Ca+2 agonists. Microinjection studies show that all three mechanisms are present and functional in cells. The emerging picture of multiplicity in Ca+2 signaling mechanisms underscores the versatility of Ca+2 in regulating diverse cellular functions.

CC 13-0 (Mammalian Biochemistry)

IT Signal transduction, biological
(cyclic ADP-ribose **modulator** and messenger functions in calcium signaling)

IT **119340-53-3**, Cyclic ADP-ribose
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(cyclic ADP-ribose **modulator** and messenger functions in calcium signaling)

IT **7440-70-2**, Calcium, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(cyclic ADP-ribose **modulator** and messenger functions in calcium signaling)

L6 ANSWER 9 OF 15 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1995:902110 HCAPLUS

DOCUMENT NUMBER: 123:335409

TITLE: Specific **modulation** of cyclic ADP-ribose-induced Ca2+ release by polyamines

AUTHOR(S): Chini, Eduardo Nunes; Beers, Kelly W.; Chini, Claudia C. S.; Dousa, Thomas P.

CORPORATE SOURCE: Renal Pathophysiol. Lab., Mayo Clinic and Foundation, Rochester, MN, 55905, USA

SOURCE: American Journal of Physiology (1995), 269(4, Pt. 1), C1042-C1047
CODEN: AJPHAP; ISSN: 0002-9513

PUBLISHER: American Physiological Society

DOCUMENT TYPE: Journal
LANGUAGE: English
AB Cyclic ADP-ribose (cADPR) is a potent mediator of Ca2+ mobilization from intracellular stores in sea urchin (Lytechinus pictus) eggs. However, the regulation of the cADPR-induced Ca2+ release system is not yet fully elucidated. Here, the authors report that spermine and related polyamines, in physiol. concns., were able to inhibit the Ca2+ release induced by cADPR in sea urchin egg homogenate bioassays, as measured using the Ca2+ indicator fluo 3, but had no effect on the Ca2+ release induced by D-myo-inositol 1,4,5-trisphosphate (IP3) or by nicotinate adenine dinucleotide phosphate (NAADP). Spermine was a more potent inhibitor of the cADPR-induced Ca2+ release than spermidine and putrescine. Spermine inhibited not only the release induced by cADPR but also the Ca2+ release induced by caffeine and ryanodine. Finally, pretreatment of the sea urchin egg homogenates with caffeine or Sr2+ and Ca2+ prevented the inhibitory effect of spermine on cADPR-induced Ca2+ release. It is proposed that polyamines, which are present in millimolar concns. in fertilized eggs, are specific inhibitors of the ryanodine channel and perhaps may serve as endogenous regulators of the cADPR-induced Ca2+ release system.
CC 12-2 (Nonmammalian Biochemistry)
IT Ion channel
(ryanodine; specific **modulation** of cyclic ADP-ribose-induced Ca2+ release by polyamines)
IT Lytechinus pictus
(specific **modulation** of cyclic ADP-ribose-induced Ca2+ release by polyamines)
IT Egg
(oocyte, specific **modulation** of cyclic ADP-ribose-induced Ca2+ release by polyamines)
IT 15662-33-6, Ryanodine
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(channel for; specific **modulation** of cyclic ADP-ribose-induced Ca2+ release by polyamines)
IT 58-08-2, Caffeine, biological studies 71-44-3, Spermine 110-60-1, Putrescine 124-20-9, Spermidine 7440-24-6, Strontium, biological studies **119340-53-3**, Cyclic ADP-ribose
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(specific **modulation** of cyclic ADP-ribose-induced Ca2+ release by polyamines)
IT **7440-70-2**, Calcium, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(specific **modulation** of cyclic ADP-ribose-induced Ca2+ release by polyamines)

L6 ANSWER 10 OF 15 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1995:898675 HCAPLUS
DOCUMENT NUMBER: 123:306965
TITLE: Agonist-stimulated cyclic ADP ribose. Endogenous **modulator** of Ca2+-induced Ca2+ release in intestinal longitudinal muscle
AUTHOR(S): Kuemmerle, John F.; Makhlouf, Gabriel M.
CORPORATE SOURCE: Med. Coll. Virginia, Virginia Commonwealth Univ., richmond, VA, 23298-0711, USA
SOURCE: Journal of Biological Chemistry (1995), 270(43), 25488-94
CODEN: JBCHA3; ISSN: 0021-9258

PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The present study examd. whether cyclic ADP-ribose (cADPR) is synthesized in response to stimulation of rabbit small intestine longitudinal muscle by agonists [cholecystokinin octapeptide CCK-8)] and modulates the activity of Ca2+ release channels. Cyclic ADPR bound with high affinity to dispersed longitudinal muscle cells (IC50 1.9 nM) and induced Ca2+ release (EC50 3.8 nM), increase in [Ca2+]i (EC50 2.0 nM), and contraction (EC50 1.1 nM); cADPR had no effect on circular muscle cells. The effects of cADPR were blocked by ruthenium red, dantrolene, and the specific antagonist, 8-amino-cADPR, and were augmented by caffeine, but were not affected by heparin. The binding of cADPR and its ability to stimulate Ca2+ release were dependent on the concn. of Ca2+. Cyclic ADPR was capable of stimulating Ca2+ release at subthreshold Ca2+ concns. (25-100 nM) and of enhancing Ca2+-induced Ca2+ release. Longitudinal muscle exts. incubated with .beta.-NAD+ produced a time-dependent increase in Ca2+-mobilizing activity identified as authentic cADPR by blockade of Ca2+ release with 8-amino-cADPR and ruthenium red. Ca2+ mobilizing activity was increased by CCK-8 in a concn.-dependent fashion. The increase induced by CCK-8 was suppressed by the CCK-A antagonist, L364,718, nifedipine, and guanyl-5'-yl thiophosphate. The study shows that ADP-ribosyl cyclase can be stimulated by agonists and that cADPR can act as an endogenous modulator of Ca2+-induced Ca2+ release.
CC 2-6 (Mammalian Hormones)
IT Biological transport
(of calcium; cholecystokinin-stimulated cyclic ADP ribose **modulates** calcium-induced calcium release in intestinal longitudinal muscle)
IT Intestine
(small, cholecystokinin-stimulated cyclic ADP ribose **modulates** calcium-induced calcium release in intestinal longitudinal muscle)
IT 25126-32-3, Cholecystokinin-8 (pig)
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(cholecystokinin-stimulated cyclic ADP ribose **modulates** calcium-induced calcium release in intestinal longitudinal muscle)
IT **7440-70-2**, Calcium, biological studies **119340-53-3**, Cyclic ADP ribose
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(cholecystokinin-stimulated cyclic ADP ribose **modulates** calcium-induced calcium release in intestinal longitudinal muscle)

L6 ANSWER 11 OF 15 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1994:405562 HCAPLUS
DOCUMENT NUMBER: 121:5562
TITLE: Cyclic ADP-ribose **modulates** Ca2+ release channels for activation by physiological Ca2+ entry in bullfrog sympathetic neurons
AUTHOR(S): Hua, Shao Ying; Tokimasa, Takayuki; Takasawa, Shin; Furuya, Yasuhito; Nohmi, Mitsuo; Okamoto, Hiroshi; Kuba, Kenji
CORPORATE SOURCE: Dep. Physiol., Saga Med. Sch., Nabeshima, 849, Japan
SOURCE: Neuron (1994), 12(5), 1073-9
CODEN: NERNET; ISSN: 0896-6273
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The authors studied the effects of cyclic ADP-ribose (cADPR) on Ca-induced

Ca release (CICR) in cultured bullfrog (Rana catesbeiana) sympathetic neurons by fura-2 fluorescence recording and patch-clamp techniques. The cADPR applied through a patch pipet augmented action potential- or depolarizing pulse-induced rises in intracellular Ca2+ without a change in Ca2+ entry initiating the responses, but not in the presence of ryanodine. Likewise, cADPR enhanced a single or oscillatory rise(s) in intracellular Ca2+ induced by caffeine. These results strongly suggest that cADPR can be an endogenous modulator of ryanodine receptors in neurons.

CC 12-6 (Nonmammalian Biochemistry)

IT **119340-53-3**, Cyclic ADP-ribose
RL: BIOL (Biological study)
(ryanodine receptor of sympathetic nerve of bullfrog regulation by)

IT **7440-70-2**, Calcium, biological studies
RL: BIOL (Biological study)
(transport of, by sympathetic nerve of bullfrog, cyclic ADP-ribose regulation of)

L6 ANSWER 12 OF 15 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1994:266393 HCAPLUS
DOCUMENT NUMBER: 120:266393
TITLE: Cyclic ADP-ribose - **modulator** of Ca2+ release from intracellular stores
AUTHOR(S): Woronczak, Jan Pawel; Baranska, Jolanta
CORPORATE SOURCE: Inst. Biol. Dos. M. Nenckiego, PAN, Warsaw, 02-093, Pol.
SOURCE: Postepy Biochemii (1993), 39(4), 210-11
CODEN: PSTBAH; ISSN: 0032-5422
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Polish

AB A review, with 15 refs., on the role of cyclic ADP-ribose in the release of Ca2+ from intracellular stores.

CC 13-0 (Mammalian Biochemistry)

IT **119340-53-3**, Cyclic ADP-ribose
RL: BIOL (Biological study)
(calcium release from intracellular stores **modulation** by)

IT **7440-70-2**, Calcium, biological studies
RL: BIOL (Biological study)
(release of, from intracellular stores, cyclic ADP-ribose **modulation** of)

L6 ANSWER 13 OF 15 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1993:251743 HCAPLUS
DOCUMENT NUMBER: 118:251743
TITLE: Potentiation of calcium- and caffeine-induced calcium release by cyclic ADP-ribose
AUTHOR(S): Lee, Hon Cheung
CORPORATE SOURCE: Dep. Physiol., Univ. Minnesota, Minneapolis, MN, 55455, USA
SOURCE: Journal of Biological Chemistry (1993), 268(1), 293-9
CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Cyclic ADP-ribose (cADPR) is a naturally occurring metabolite of NAD+ that is as potent as inositol 1,4,5-trisphosphate (IP3) in mobilizing Ca2+ in sea urchin eggs. Previous pharmacol. evidence suggests that cADPR acts through a system similar to the Ca2+-induced Ca2+ release (CICR). In the presence of low concns. of cADPR, addn. of Ca2+ to egg homogenates stimulated further release of Ca2+ in a concn.-dependent manner. In the absence of cADPR, no induced release was seen, and the added Ca2+ was, instead, sequestered by a thapsigargin-sensitive transport system. High

concns. of strontium (>50 mM) could also induce Ca2+ release. The effective concns. of Sr2+, however, were reduced 10-20-fold in the presence of low concns. of cADPR. Barium, at up to 0.4 mM, did not stimulate Ca2+ release with or without cADPR. The potentiation between divalent cations and cADPR was mutual since the Ca2+ releasing activity of cADPR was also increased in the presence of strontium. Ionomycin and thapsigargin both released Ca2+ but neither potentiated Ca2+ release induced by divalent cations. Caffeine also released Ca2+ in a concn.-dependent manner, and its potency was greatly increased by low concns. of cADPR, while no such simulation was seen with IP3. Conversely, low concns. of caffeine that were not sufficient to release Ca2+ increased the effectiveness of cADPR 10-fold. Isocaffeine, an isomer of caffeine, was four to five times less effective, demonstrating the specificity of the caffeine effect. These results suggest that cADPR can function as an endogenous regulator of CICR in eggs.

CC 12-6 (Nonmammalian Biochemistry)

IT Egg
(calcium-induced calcium release in, cyclic ADP-ribose **modulation** of)

IT Cations
(divalent, calcium release induction by, in egg, cyclic ADP-ribose **modulation** of)

IT 58-08-2, Caffeine, biological studies 7440-24-6, Strontium, biological studies 7440-39-3, Barium, biological studies **7440-70-2**, Calcium, biological studies
RL: BIOL (Biological study)
(calcium release induction by, in egg, cyclic ADP-ribose **modulation** of)

IT **119340-53-3**
RL: BIOL (Biological study)
(calcium-induced calcium release **modulation** by, in egg)

L6 ANSWER 14 OF 15 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1992:568118 HCAPLUS
DOCUMENT NUMBER: 117:168118
TITLE: Calcium-induced Ca2+ release and its **modulation** by cyclic ADP-ribose
AUTHOR(S): Galione, Antony
CORPORATE SOURCE: Dep. Pharmacol., Oxford Univ., Oxford, OX1 3QT, UK
SOURCE: Trends in Pharmacological Sciences (1992), 13(8), 304-6
CODEN: TPHSDY; ISSN: 0165-6147
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review, with 27 refs., suggesting that cADP-ribose acts on a sep. Ca2+-release mechanism from that activated by inositol trisphosphate (IP3). It may modulate a ryanodine-sensitive, but IP3-insensitive, Ca2+ channel of the endoplasmic reticulum.

CC 13-0 (Mammalian Biochemistry)
Section cross-reference(s): 2

IT Biological transport
(channel-mediated, of calcium, cADP-ribose **modulation** of)

IT **119340-53-3**
RL: BIOL (Biological study)
(calcium release **modulation** by)

IT **7440-70-2**, Calcium, biological studies
RL: BIOL (Biological study)
(release of, calcium induction of, cADP-ribose **modulation** of)

L6 ANSWER 15 OF 15 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1991:628841 HCAPLUS
DOCUMENT NUMBER: 115:228841
TITLE: Calcium-induced Ca2+ release in sea urchin egg homogenates: **modulation** by cyclic ADP-ribose
AUTHOR(S): Galione, Antony; Lee, Hon Cheung; Busa, William B.
CORPORATE SOURCE: Dep. Biol., Johns Hopkins Univ., Baltimore, MD, 21218, USA
SOURCE: Science (Washington, DC, United States) (1991), 253(5024), 1143-6
CODEN: SCIEAS; ISSN: 0036-8075
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Calcium-induced calcium release (CICR) may function widely in calcium-mediated cell signaling, but has been most thoroughly characterized in muscle cells. In a homogenate of sea urchin eggs, which display transients in the intracellular free calcium concn. ([Ca2+]i) during fertilization and anaphase, addn. of Ca2+ triggered CICR. Ca2+ release was also induced by the CICR modulators ryanodine and caffeine. Responses to both Ca2+ and CICR modulators (but not Ca2+ release mediated by inositol 1,4,5-trisphosphate) were inhibited by procain and ruthenium red, inhibitors of CICR. Intact eggs also displayed transients of [Ca2+]i when microinjected with ryanodine. Cyclic ADP-ribose, a metabolite with potent Ca2+-releasing properties, appears to act by way of the CICR mechanism and may thus be an endogenous modulator of CICR. A CICR mechanism is present in these nonmuscle cells as is assumed in various models of intracellular Ca2+ wave propagation.

CC 12-6 (Nonmammalian Biochemistry)
Section cross-reference(s): 13

IT Egg
(calcium release by, calcium-induced, of sea urchin, cADP-ribose **modulation** of)

IT Sea urchin
(calcium-induced calcium release in eggs of, cADP-ribose **modulation** of)

IT **119340-53-3**
RL: BIOL (Biological study)
(calcium-induced calcium release in sea urchin eggs **modulation** by)

IT **7440-70-2**, Calcium, biological studies
RL: BIOL (Biological study)
(release of, in sea urchin eggs, calcium-induced, cADP-ribose **modulation** of)

L13 ANSWER 1 OF 3 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:283457 HCAPLUS
DOCUMENT NUMBER: 137:60713
TITLE: Role of FKBP12.6 in cADPR-induced activation of reconstituted ryanodine receptors from arterial smooth muscle
AUTHOR(S): Tang, Wang-Xian; Chen, Ya-Fei; Zou, Ai-Ping; Campbell, William B.; Li, Pin-Lan
CORPORATE SOURCE: Research Institute of Liver Disease, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, 430030, Peop. Rep. China
SOURCE: American Journal of Physiology (2002), 282(4, Pt. 2), H1304-H1310

CODEN: AJPHAP; ISSN: 0002-9513
PUBLISHER: American Physiological Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB CADP ribose (cADPR) serves as second messenger to activate the ryanodine receptors (RyRs) of the sarcoplasmic reticulum (SR) and mobilize intracellular Ca2+ in vascular smooth muscle cells. However, the mechanisms mediating the effect of cADPR remain unknown. The present study was designed to det. whether FK-506 binding protein 12.6 (FKBP12.6), an accessory protein of the RyRs, plays a role in cADPR-induced activation of the RyRs. A 12.6-kDa protein was detected in bovine coronary arterial smooth muscle (BCASM) and cultured CASM cells by being immunoblotted with an antibody against FKBP12, which also reacted with FKBP12.6. With the use of planar lipid bilayer clamping techniques, FK-506 (0.01-10 .mu.M) significantly increased the open probability (NPO) of reconstituted RyR/Ca2+ release channels from the SR of CASM. This FK-506-induced activation of RyR/Ca2+ release channels was abolished by pretreatment with anti-FKBP12 antibody. The RyRs activator cADPR (0.1-10 .mu.M) markedly increased the activity of RyR/Ca2+ release channels. In the presence of FK-506, cADPR did not further increase the NPO of RyR/Ca2+ release channels. Addn. of anti-FKBP12 antibody also completely blocked cADPR-induced activation of these channels, and removal of FKBP12.6 by preincubation with FK-506 and subsequent gradient centrifugation abolished cADPR-induced increase in the NPO of RyR/Ca2+ release channels. We conclude that FKBP12.6 plays a crit. role in mediating cADPR-induced activation of RyR/Ca2+ release channels from the SR of BCASM.

CC 13-2 (Mammalian Biochemistry)
ST FKBP126 cADPribose **calcium** ryanodine receptor smooth muscle coronary artery
IT **Immunophilins**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(FKBP (FK 506-binding protein), FKBP12.6; role of FKBP12.6 in cADP ribose-induced activation of reconstituted ryanodine receptors from arterial smooth muscle)
IT Biological transport
(**calcium**; role of FKBP12.6 in cADP ribose-induced activation of reconstituted ryanodine receptors from arterial smooth muscle)
IT **119340-53-3**, Cyclic ADP-ribose
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(role of FKBP12.6 in cADP ribose-induced activation of reconstituted ryanodine receptors from arterial smooth muscle)
IT **7440-70-2**, **Calcium**, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(transport; role of FKBP12.6 in cADP ribose-induced activation of reconstituted ryanodine receptors from arterial smooth muscle)
REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 2 OF 3 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2002:122798 HCAPLUS
DOCUMENT NUMBER: 136:177974
TITLE: Nicotinic acid adenine dinucleotide phosphate (NAADP) analogs for modulating T-cell activity
INVENTOR(S): Potter, Barry V. L.; Guse, Andreas H.; Mayr, Georg W.; Berg, Ingeborg
PATENT ASSIGNEE(S): University of Bath, UK
SOURCE: PCT Int. Appl., 83 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002011736	A1	20020214	WO 2001-GB3440	20010731

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

AU 2001075732	A5	20020218	AU 2001-75732	20010731

PRIORITY APPLN. INFO.: GB 2000-19234 A 20000804
WO 2001-GB3440 W 20010731

OTHER SOURCE(S): MARPAT 136:177974

AB A method for modulating T cell activity by modulating the intracellular concn. and/or activity of NAADP+, compds. capable of modulating the effect of NAADP+ on T cell Ca+2 levels, and methods for identifying such compds., are described. Prepn. of 8-bromo-nicotinic acid adenine dinucleotide phosphate is described.

IC ICM A61K031-70
ICS C07H021-02; C07H019-207

CC 1-7 (Pharmacology)
Section cross-reference(s): 33

ST nicotinic acid adenine dinucleotide phosphate analog T cell **immunomodulator**; NAADP analog prepn T cell **immunomodulator** ; screening **immunomodulator** T cell NAADP analog; bromonicotinic acid adenine dinucleotide phosphate prepn T cell **immunomodulator**

IT Addison's disease
Antirheumatic agents
Autoimmune disease
Drug screening
Hepatitis
Immunomodulators
Lupus erythematosus
Myasthenia gravis
Signal transduction, biological
T cell (lymphocyte)
Transplant rejection
(NAADP analogs for modulating T-cell activity)

IT **Immune** tolerance
(anergy, T-cell; NAADP analogs for modulating T-cell activity)

IT **Immunity**
(**disorder**; NAADP analogs for modulating T-cell activity)

IT 5502-96-5, Nicotinic acid adenine dinucleotide phosphate **7440-70-2**, **Calcium**, biological studies 88269-39-0, Inositol-1,4,5-trisphosphate **119340-53-3**, CADPR
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(NAADP analogs for modulating T-cell activity)

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 3 OF 3 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:627781 HCAPLUS
DOCUMENT NUMBER: 127:291068
TITLE: Intramolecular ADP-ribose transfer reactions and

calcium signaling. Potential role of 2'-phospho-cyclic ADP-ribose in oxidative stress

AUTHOR(S): Vu, Chinh Q.; Coyle, Donna L.; Tai, Hsin-Hsiung; Jacobson, Elaine L.; Jacobson, Myron K.
CORPORATE SOURCE: Division of Medicinal Chemistry and Pharmaceutics, College of Pharmacy, University of Kentucky, Lexington, KY, 40536, USA

SOURCE: Advances in Experimental Medicine and Biology (1997), 419(ADP-Ribosylation in Animal Tissues), 381-388
CODEN: AEMBAP; ISSN: 0065-2598
PUBLISHER: Plenum
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Intramol. ADP-ribose transfer reactions result in the formation of cyclic ADP-ribose (cADPR) and 2'-phospho-cyclic ADP-ribose (P-cADPR) from NAD and NADP, resp. The potent Ca2+ releasing activity of these cyclic nucleotides has led to the postulation that they function as second messengers of Ca2+ signaling. The synthesis and hydrolysis of cADPR and P-cADPR are catalyzed by NAD(P) glycohydrolases, but the metabolic signals that regulate their metab. are poorly understood. To investigate the physiol. roles of cADPR and P-cADPR, it is essential to have methods that allow the routine measurement of these nucleotides in cellular systems. As described here, a sensitive and selective RIA for cADPR has been adapted to search for the natural occurrence of P-cADPR in mammalian tissues. Perchloric acid exts. prepd. from bovine tissues and purified by anion exchange chromatog. were found to contain immunoreactive material which was identified as P-cADPR. P-cADPR may play an important role in oxidative stress as a link between NADP(H) metab. and alteration of intracellular Ca2+ homeostasis.

CC 13-2 (Mammalian Biochemistry)
ST oxidative stress **calcium** ADPribose transfer
IT Oxidative stress, biological
Second messenger system
(intramol. ADP-ribose transfer reactions and **calcium** signaling and potential role of phospho-cyclic ADP-ribose in oxidative stress)
IT **Immunoassay**
(radioimmunoassay; intramol. ADP-ribose transfer reactions and **calcium** signaling and potential role of phospho-cyclic ADP-ribose in oxidative stress)
IT 53-59-8, NADP 53-84-9, NAD **7440-70-2**, **Calcium**, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(intramol. ADP-ribose transfer reactions and **calcium** signaling and potential role of phospho-cyclic ADP-ribose in oxidative stress)
IT 20762-30-5, ADP-ribose **119340-53-3**, Cyclic ADP-ribose
RL: BPR (Biological process); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)
(intramol. ADP-ribose transfer reactions and **calcium** signaling and potential role of phospho-cyclic ADP-ribose in oxidative stress)

L18 ANSWER 1 OF 26 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:783699 HCAPLUS

DOCUMENT NUMBER: 136:49822
TITLE: Lack of effect of cADP-ribose and NAADP on the activity of skeletal muscle and heart **ryanodine receptors**
AUTHOR(S): Copello, J. A.; Qi, Y.; Jeyakumar, L. H.; Ogunbunmi, E.; Fleischer, S.
CORPORATE SOURCE: Department of Molecular Biology, Vanderbilt University, Nashville, TN, USA
SOURCE: Cell Calcium (2001), 30(4), 269-284
CODEN: CECADV; ISSN: 0143-4160
PUBLISHER: Harcourt Publishers Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The calcium release channels/ryanodine receptors (RyRs) are potential/putative targets of cADPR (cyclic ADP-ribose) action in many tissue systems. In striated muscles, where RyRs predominate, cADPR action on these channels is controversial. Here cADPR modulation of cardiac and skeletal muscle RyR channels was tested. We considered factors reported as necessary for cADPR action, such as the presence of calmodulin and/or FK binding proteins (FKBPs). We found: (1) The RyR channel isoforms were insensitive to cADPR (or its metabolite NAADP [nicotinic acid adenine dinucleotide phosphate]) under all conditions examd., as studied by: (1a) single channel recordings in planar lipid bilayers; (1b) macroscopic behavior of the RyRs in sarcoplasmic reticulum (SR) microsomes (including crude microsome prepns. likely to retain putative cADPR cofactors) at room temp. and at 37.degree.C (net energized Ca2+ uptake or passive Ca2+ leak); (2) [32P]cADPR did not bind significantly to SR microsomes; (3) cADPR did not affect FKBP assocn. to SR membranes. We conclude that cADPR does not interact directly with RyRs or RyR-assocd. SR proteins. Our results under in vitro conditions suggest that cADPR effects on Ca2+ signaling obsd. in vivo in mammalian striated muscle cells may reflect indirect modulation of RyRs or RyR-independent Ca2+ release systems.

CC 6-1 (General Biochemistry)
ST cADP ribose NAADP **ryanodine receptor calcium** transport muscle heart
IT **Immunophilins**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(FKBP (FK 506-binding protein); lack of effect of cADP-ribose and NAADP on activity of skeletal muscle and heart **ryanodine receptors** and on RyR-assocd. SR proteins)
IT Membrane, biological
(bilayer; lack of effect of cADP-ribose and NAADP on activity of skeletal muscle and heart **ryanodine receptors** and on RyR-assocd. SR proteins)
IT **Calcium channel**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**calcium**-release **channel**; lack of effect of cADP-ribose and NAADP on activity of skeletal muscle and heart **ryanodine receptors** and on RyR-assocd. SR proteins)
IT Biological transport
(**calcium**; lack of effect of cADP-ribose and NAADP on activity of skeletal muscle and heart **ryanodine receptors** and on RyR-assocd. SR proteins)
IT Heart
Microsome
Muscle
(lack of effect of cADP-ribose and NAADP on activity of skeletal muscle and heart **ryanodine receptors** and on RyR-assocd. SR proteins)
IT Calmodulins

Ryanodine receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(lack of effect of cADP-ribose and NAADP on activity of skeletal muscle and heart **ryanodine receptors** and on RyR-assocd. SR proteins)

IT Endoplasmic reticulum
(sarcoplasmic reticulum; lack of effect of cADP-ribose and NAADP on activity of skeletal muscle and heart **ryanodine receptors** and on RyR-assocd. SR proteins)

IT 5502-96-5, Nicotinic acid adenine dinucleotide phosphate 20762-30-5, ADP-ribose
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(lack of effect of cADP-ribose and NAADP on activity of skeletal muscle and heart **ryanodine receptors** and on RyR-assocd. SR proteins)

IT **7440-70-2, Calcium**, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(transport; lack of effect of cADP-ribose and NAADP on activity of skeletal muscle and heart **ryanodine receptors** and on RyR-assocd. SR proteins)

REFERENCE COUNT: 58 THERE ARE 58 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 2 OF 26 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:775265 HCAPLUS
DOCUMENT NUMBER: 136:132090
TITLE: Investigation of differentially expressed genes during the development of mouse cerebellum
AUTHOR(S): Kagami, Yoshihiro; Furuichi, Teiichi
CORPORATE SOURCE: Laboratory for Molecular Neurogenesis, Brain Science Institute, RIKEN, Wako, 351-0198, Japan
SOURCE: Gene Expression Patterns (2001), 1(1), 39-59
CODEN: GEPEAD; ISSN: 1567-133X
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Before the discovery of DNA microarray and DNA chip technol., the expression of only a small no. of genes could be analyzed at a time. Currently, such technol. allows us the simultaneous anal. of a large no. of genes to systematically monitor their expression patterns that may be assocd. with various biol. phenomena. We utilized the Affymetrix GeneChip Mu11K to analyze the gene expression profile in developing mouse cerebellum to assist in the understanding of the genetic basis of cerebellar development in mice. Our anal. showed 81.6% (10.321/12.654) of the genes represented on the GeneChip were expressed in the postnatal cerebellum, and among those, 8.7% (897/10.321) were differentially expressed with more than a two-fold change in their max. and min. expression levels during the developmental time course. Further anal. of the differentially expressed genes that were clustered in terms of their expression patterns and the function of their encoded products revealed an aspect of the genetic foundation that lies beneath the cellular events and neural network formation that takes place during the development of the mouse cerebellum.

CC 13-3 (Mammalian Biochemistry)
Section cross-reference(s): 3

IT Gene, animal
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**Calcium**/calmodulin-dependent protein kinase II, .beta.-encoding; anal. of differentially expressed genes during development of mouse cerebellum using DNA microarray/chip technol.)

IT **Immunophilins**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(FKBP (FK 506-binding protein), FK506 binding protein 5; anal. of differentially expressed genes during development of mouse cerebellum using DNA microarray/chip technol.)

IT Gene, animal
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(Ryr2, **ryanodine receptor** type2-encoding; anal. of differentially expressed genes during development of mouse cerebellum using DNA microarray/chip technol.)

IT **Ryanodine receptors**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(Ryr2, **ryanodine receptor** type2; anal. of differentially expressed genes during development of mouse cerebellum using DNA microarray/chip technol.)

IT **Calcium**-binding proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(S-100, .beta. polypeptide, neural; anal. of differentially expressed genes during development of mouse cerebellum using DNA microarray/chip technol.)

IT Gene, animal
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(S100 **calcium**-binding protein A13-encoding; anal. of differentially expressed genes during development of mouse cerebellum using DNA microarray/chip technol.)

IT **Calcium**-binding proteins.
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(S100 **calcium**-binding protein A13; anal. of differentially expressed genes during development of mouse cerebellum using DNA microarray/chip technol.)

IT Gene, animal
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**calcium**-activated potassium **channel**-encoding; anal. of differentially expressed genes during development of mouse cerebellum using DNA microarray/chip technol.)

IT Potassium **channel**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**calcium**-activated potassium **channel**; anal. of differentially expressed genes during development of mouse cerebellum using DNA microarray/chip technol.)

IT **Calcium**-binding proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(neural visinin-like Ca2+-binding protein type 1 (NVP-1); anal. of differentially expressed genes during development of mouse cerebellum using DNA microarray/chip technol.)

IT Gene, animal
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(sarco(endo)plasmic reticulum **calcium** ATPase (SERCA2)-encoding; anal. of differentially expressed genes during development of mouse cerebellum using DNA microarray/chip technol.)

IT Gene, animal
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(taipoxin-assocd. **calcium** binding protein 49-encoding; anal. of differentially expressed genes during development of mouse cerebellum using DNA microarray/chip technol.)

IT **Calcium**-binding proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(taipoxin-assocd. **calcium** binding protein 49; anal. of differentially expressed genes during development of mouse cerebellum using DNA microarray/chip technol.)

IT 9000-83-3, Vacuolar ATPase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(calcium-dependent, SERCA2 and SERCA3b; proton-translocating, vacuolar ATPase subunit A; anal. of differentially expressed genes during development of mouse cerebellum using DNA microarray/chip technol.)
REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 3 OF 26 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:676999 HCAPLUS
DOCUMENT NUMBER: 135:252790
TITLE: Single nucleotide polymorphisms in human genes
INVENTOR(S): Cargill, Michele; Ireland, James S.; Lander, Eric S.
PATENT ASSIGNEE(S): Whitehead Institute for Biomedical Research, USA
SOURCE: PCT Int. Appl., 145 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001066800	A2	20010913	WO 2001-US7268	20010307
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 2002032319	A1	20020314	US 2001-801274	20010307

PRIORITY APPLN. INFO.: US 2000-187510P P 20000307
US 2000-206129P P 20000522

AB The invention provides nucleic acid segments of the human genome, particularly nucleic acid segments from genes including polymorphic sites. The polymorphisms were identified by resequencing of target sequences from individuals of diverse ethnic and geog. backgrounds by hybridization to probes immobilized to microfabricated arrays. Some of the single nucleotide polymorphisms (SNPs) specify a different amino acid sequence, some are silent or are in noncoding regions, and some specify a stop signal in protein translation. Allele-specific primers and probes hybridizing to regions flanking or contg. these sites are also provided. The nucleic acids, primers and probes are used in applications such as phenotype correlations, forensics, paternity testing, medicine and genetic anal.
IC ICM C12Q001-68
CC 3-3 (Biochemical Genetics)
Section cross-reference(s): 13
IT **Immunoglobulin** receptors
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BUU (Biological use, unclassified); PRP (Properties); BIOL (Biological study); OCCU (Occurrence); USES (Uses)
(IgG type IIB1; single nucleotide polymorphisms in human genes)
IT **Calcium channel**
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BUU (Biological use, unclassified); PRP (Properties); BIOL (Biological study);

OCCU (Occurrence); USES (Uses)
(single nucleotide polymorphisms in human genes)

IT **Ryanodine receptors**
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BUU (Biological use, unclassified); PRP (Properties); BIOL (Biological study); OCCU (Occurrence); USES (Uses)
(single nucleotide polymorphisms in human genes)

L18 ANSWER 4 OF 26 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:661465 HCAPLUS
DOCUMENT NUMBER: 135:221321
TITLE: Maurocalcine, analogs thereof, and their therapeutic use as **immunosuppressants** and in the treatment of **calcium channel** dysfunction-related diseases
INVENTOR(S): Kharrat, Riad; Mabrouk, Kamel; El-Ayeb, Mohammed; Rochat, Herve; Sabatier, Jean-Marc
PATENT ASSIGNEE(S): Cellpep S.A., Fr.
SOURCE: PCT Int. Appl., 10 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001064724	A2	20010907	WO 2001-EP2582	20010305
WO 2001064724	A3	20020418		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: GB 2000-5124 A 20000303

AB Maurocalcine, a novel toxin isolated from the venom of the Tunisian chactidae scorpion Scorpio maurus palmatus, has the amino acid sequence GDCLPHLKLCKENKDCCSKKCKRRGTNIEKRCR. It potently and reversibly modifies channel gating behavior of type 1 ryanodine receptor (RyR1) by inducing prominent subconductance behavior. Maurocalcine and its bioactive structural analogs - preferably those contg. the KKCKRR motif corresponding to part of the II-III loop of the alpha1S subunit of the voltage-dependent skeletal muscle calcium channel dihydropyridine receptor - appear to possess a therapeutic potential, notably as candidate immunosuppressive drugs, and for the treatment of pathologies in humans that may involve a dysfunction of calcium channels.

IC ICM C07K014-435
CC 1-12 (Pharmacology)
ST maurocalcine **immunosuppressant calcium channel** disease therapeutic; **ryanodine receptor** maurocalcine therapeutic
IT **Immunosuppressants**
(maurocalcine and analogs as **immunosuppressants** and in treatment of **calcium channel** dysfunction-related diseases)
IT **Calcium channel**

Ryanodine receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(maurocalcine and analogs as **immunosuppressants** and in treatment of **calcium channel** dysfunction-related diseases)
IT 269745-22-4P, Maurocalcine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(maurocalcine and analogs as **immunosuppressants** and in treatment of **calcium channel** dysfunction-related diseases)
IT 269745-22-4D, Maurocalcine, analogs
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(maurocalcine and analogs as **immunosuppressants** and in treatment of **calcium channel** dysfunction-related diseases)
IT 358335-02-1
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(maurocalcine and analogs as **immunosuppressants** and in treatment of **calcium channel** dysfunction-related diseases)
IT 359009-91-9
RL: PRP (Properties)
(unclaimed protein sequence; maurocalcine, analogs thereof, and their therapeutic use as **immunosuppressants** and in the treatment of **calcium channel** dysfunction-related diseases)

L18 ANSWER 5 OF 26 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:645868 HCAPLUS
DOCUMENT NUMBER: 135:240434
TITLE: Interaction of **immunophilin** FKBP and Ca2+ release channel
AUTHOR(S): Onoue, Hitoshi; Itonaga, Yasuhiro; Ito, Yushi
CORPORATE SOURCE: Dep. Pharmacol., Grad. Sch. Med. Sci., Kyushu Univ., Fukuoka, 812-8582, Japan
SOURCE: Fukuoka Igaku Zasshi (2001), 92(7), 272-277
CODEN: FKIZA4; ISSN: 0016-254X
PUBLISHER: Fukuoka Igakkai
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese
AB A review with 3 refs., on functions of immunophilin FK506-binding protein (FKBP) as a calcium release channel regulatory factor, focusing on interaction of FKBP with the ryanodine receptor, a intracellular calcium release channel.
CC 15-0 (Immunochemistry)
Section cross-reference(s): 1
ST review **immunophilin** FKBP **calcium channel**; **ryanodine receptor** FKBP review
IT **Immunophilins**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(FKBP (FK506-binding protein); interaction between **immunophilin** FKBP and **calcium** release **channel**)

IT Molecular association
(interaction between **immunophilin** FKBP and **calcium** release **channel**)
IT **Ryanodine receptors**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(interaction between **immunophilin** FKBP and **calcium** release **channel**)
IT **Calcium channel**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(interaction between **immunophilin** FKBP and **calcium** release **channel**)
IT **7440-70-2, Calcium**, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(interaction between **immunophilin** FKBP and **calcium** release **channel**)
IT 104987-11-3, FK 506
RL: BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(interaction between **immunophilin** FKBP and **calcium** release **channel**)

L18 ANSWER 6 OF 26 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:360024 HCAPLUS
DOCUMENT NUMBER: 134:361383
TITLE: Methods for treatment of human Huntington's disease and methods of screening for active agents
INVENTOR(S): Olson, James M.; Luthi-Carter, Ruth; Young, Anne; Strand, Andrew
PATENT ASSIGNEE(S): Fred Hutchinson Cancer Research Center, USA; The General Hospital Corporation
SOURCE: PCT Int. Appl., 46 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001034633	A2	20010517	WO 2000-US30900	20001110
WO 2001034633	A3	20020110		
W: AU, CA, JP, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR				
AU 2001017602	A5	20010606	AU 2001-17602	20001110
PRIORITY APPLN. INFO.:			US 1999-165079P P	19991112
			WO 2000-US30900 W	20001110

AB Genes modulated by the expression of a mutant huntington protein assocd. with Huntington's Disease have been detd. A profile of mRNAs that are modulated has been established as neurodegeneration progresses through the disease. Levels of mRNA encoding components of neurotransmitters, calcium and retinoid signaling pathways at both early and late symptomatic disease states have been established. Methods for the treatment or amelioration of disease have been detd. based on the mRNA profile detd. Further, methods for screening for agents active in ameliorating and/or preventing progression of Huntington's Disease can be detd. by examg. changes in the

level of expression of the mRNAs and/or proteins of the Huntington's Disease profile of the present invention.

IC ICM C07K

CC 1-11 (Pharmacology)
Section cross-reference(s): 14

IT **Immunophilins**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(P59, gene encoding; methods for treatment of human Huntington's disease and drug screening in relation to gene expression related to signaling modulated by mutant huntington protein)

IT **Ryanodine receptors**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(RyR1, gene encoding; methods for treatment of human Huntington's disease and drug screening in relation to gene expression related to signaling modulated by mutant huntington protein)

IT Inositol 1,4,5-trisphosphate receptors
Ryanodine receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(agonists and antagonists and gene encoding; methods for treatment of human Huntington's disease and drug screening in relation to gene expression related to signaling modulated by mutant huntington protein)

IT Ion **channel** openers
(**calcium**; methods for treatment of human Huntington's disease and drug screening in relation to gene expression related to signaling modulated by mutant huntington protein)

IT **Calcium**-binding proteins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(hippocalcin, gene encoding; methods for treatment of human Huntington's disease and drug screening in relation to gene expression related to signaling modulated by mutant huntington protein)

IT **Calcium**-binding proteins
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(methods for treatment of human Huntington's disease and drug screening in relation to gene expression related to signaling modulated by mutant huntington protein)

IT **Calcium channel**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(voltage-dependent, .beta.3 subunit, gene encoding; methods for treatment of human Huntington's disease and drug screening in relation to gene expression related to signaling modulated by mutant huntington protein)

IT 9000-83-3, ATPase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**calcium**- and proton-transporting, genes encoding and enhancers; methods for treatment of human Huntington's disease and drug screening in relation to gene expression related to signaling modulated by mutant huntington protein)

IT 60-92-4, CAMP **7440-70-2**, **Calcium**, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(signaling pathway, modulators of; methods for treatment of human Huntington's disease and drug screening in relation to gene expression related to signaling modulated by mutant huntington protein)

L18 ANSWER 7 OF 26 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:320060 HCAPLUS
DOCUMENT NUMBER: 134:339179
TITLE: Nucleic acids and proteins associated with cancer as antitumor targets
INVENTOR(S): Burmer, Glenna C.; Brown, Joseph P.; Pritchard, David
PATENT ASSIGNEE(S): Lifespan Biosciences, Inc., USA
SOURCE: PCT Int. Appl., 98 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001030964	A2	20010503	WO 2000-US29126	20001020
WO 2001030964	A3	20010809		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 2001013397	A5	20010508	AU 2001-13397	20001020

PRIORITY APPLN. INFO.: US 1999-161232P P 19991022
US 2000-693783 A 20001019
WO 2000-US29126 W 20001020

AB This invention relates to the discovery of nucleic acids assocd. with cell proliferation, neoplasia, cell transformation, malignant tumor formation and metastasis and uses therefor. The present invention provides a method for cancer diagnosing by detecting the overexpression or the underexpression of a cancer-assocd. mRNA in the tissue of interest, preferably in liver, breast, prostate, kidney and colon. In another aspect, the invention provides methods for arresting cancer and a method for identifying a modulators of cancer development.

ICI C12
CC 14-1 (Mammalian Pathological Biochemistry)
Section cross-reference(s): 1, 3
IT **Calcium channel**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(ALPH, neuroendocrine/.beta.-cell type, gene for; nucleic acids and proteins assocd. with cancer as antitumor targets)
IT **Calcium**-binding proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(I, gene for; nucleic acids and proteins assocd. with cancer as antitumor targets)
IT **Calcium channel**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(L-type, dihydropyridine-sensitive, CACML1A3 gene for; nucleic acids and proteins assocd. with cancer as antitumor targets)
IT **Calcium channel**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(L-type, dihydropyridine-sensitive, gene for; nucleic acids and proteins assocd. with cancer as antitumor targets)
IT **Calcium channel**

RL: BSU (Biological study, unclassified); BIOL (Biological study)
(L-type, .alpha.1 subunit, gene for; nucleic acids and proteins assocd. with cancer as antitumor targets)

IT APC protein
Aggrecans
CD86 (antigen)
Calnexin
Epidermal growth factor receptors
Insulin receptors
Insulin-like growth factor I receptors
Mineralocorticoid receptors
Osteonectin
Osteopontin
Porins
Prostacyclin receptors
Retinoic acid receptors
Rhodopsins
Ryanodine receptors
Thromboxane receptors
Titins
VIP receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(gene for; nucleic acids and proteins assocd. with cancer as antitumor targets)

IT Proteins, specific or class
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(histidine-rich, **calcium**-binding, sarcoplasmic reticulum, gene for; nucleic acids and proteins assocd. with cancer as antitumor targets)

IT **Immunoglobulins**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(light chains, variable region, gene for; nucleic acids and proteins assocd. with cancer as antitumor targets)

IT Antitumor agents
Drug screening
Gene therapy
Immunoassay
Kidney, neoplasm
Liver, neoplasm
Molecular cloning
(nucleic acids and proteins assocd. with cancer as antitumor targets)

L18 ANSWER 8 OF 26 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:153076 HCAPLUS
DOCUMENT NUMBER: 134:219133
TITLE: Recognition force microscopy/spectroscopy of ion channels: applications to the skeletal muscle Ca2+ release channel (RYR1)
AUTHOR(S): Kada, G.; Blayney, L.; Jeyakumar, L. H.; Kienberger, F.; Pastushenko, V. Ph.; Fleischer, S.; Schindler, H.; Lai, F. A.; Hinterdorfer, P.
CORPORATE SOURCE: Institute for Biophysics, University of Linz, Linz, A-4040, Austria
SOURCE: Ultramicroscopy (2001), 86(1/2), 129-137
CODEN: ULTRD6; ISSN: 0304-3991
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The skeletal muscle Ca2+ release channel (ryanodine receptor 1, RYR1) plays an important role in the excitation-contraction coupling process.

We purified ryanodine receptor type 1 from rabbit white muscle and adsorbed it to mica sheets with the cytoplasmic side facing up. Single receptors of uniformly distributed size and shape of 10-12 nm height and 40-50 nm width, and occasionally some aggregates were seen in contact mode AFM images. These immobilized RYR1 were specifically recognized by rabbit anti-RYR1 (antibody#8) with at least 30% efficiency, as measured by an enzyme immunoassay with goat-anti-rabbit. Single specific antibody-antigen recognition events were detected with AFM tips to which an antibody#8 was tethered. In linear scans, the occurrence of antibody-antigen binding showed significant lateral dependence, which allowed for the localization of binding sites with nm resoln. Variation of the loading rate in force spectroscopy expts. revealed a logarithmic dependence of the unbinding forces, ranging from 42 to 73 pN. From this dependence, a bond width of the binding pocket of L = 0.2 nm and a kinetic off-rate of koff = 12.7 s-1 was detd.

CC 9-4 (Biochemical Methods)

ST **ryanodine receptor** recognition force microscopy

IT **Immunoassay**
(enzyme; recognition force microscopy/spectroscopy of ion channels)

IT **Ryanodine receptors**
RL: ARU (Analytical role, unclassified); ANST (Analytical study)
(recognition force microscopy/spectroscopy of ion channels)

IT **7440-70-2, Calcium**, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(recognition force microscopy/spectroscopy of ion **channels**)

REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 9 OF 26 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:91507 HCAPLUS
DOCUMENT NUMBER: 134:159189
TITLE: SH3-binding peptides specific for the Src-family of proteins
INVENTOR(S): Sparks, Andrew B.; Kay, Brian K.; Thorn, Judith M.; Quilliam, Lawrence A.; Der, Channing J.; Fowlkes, Dana M.; Rider, James E.
PATENT ASSIGNEE(S): University of North Carolina at Chapel Hill, USA; Cytogen Corp.
SOURCE: U.S., 150 pp., Cont.-in-part of U.S. Ser. No. 483,555.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6184205	B1	20010206	US 1996-602999	19960216
US 6303574	B1	20011016	US 1994-278865	19940722
CA 2195629	AA	19960208	CA 1995-2195629	19950724
CA 2246378	AA	19970821	CA 1997-2246378	19970214
WO 9730074	A1	19970821	WO 1997-US2298	19970214

W: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, HU, IL, IS, JP, KG, KP, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

AU 9722723 A1 19970902 AU 1997-22723 19970214
AU 726263 B2 20001102
EP 897392 A1 19990224 EP 1997-905952 19970214
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI
JP 2000506522 T2 20000530 JP 1997-529492 19970214
US 6432920 B1 20020813 US 2000-500124 20000208
US 2002091085 A1 20020711 US 2001-938315 20010823
PRIORITY APPLN. INFO.: US 1994-278865 A2 19940722
US 1995-483555 A2 19950607
US 1996-602999 A 19960216
WO 1997-US2298 W 19970214

AB Peptides having general and specific binding affinities for the Src homol. region 3 (SH3) domains of proteins are disclosed in the present invention. In particular, SH3 binding peptides have been isolated from phage-displayed random peptide libraries which had been screened for isolates that bind to bacterial fusion proteins having an SH3 domain and glutathione S-transferase (GST). Preferred peptides are disclosed which comprise a core 7-mer sequence (preferably, a consensus motif) and two or more, preferably at least six, addnl. amino acid residues flanking the core sequence, for a total length of 9, preferably at least 13, amino acid residues and no more than about 45 amino acid residues. Such peptides manifest preferential binding affinities for certain SH3 domains. The preferred peptides exhibit specific binding affinities for the Src-family of proteins, including Grb2, Yes, Fyn, Lyn, Lck, Hck, and Fgr. In vitro and in vivo results are presented which demonstrate the biochem. activity of such peptides. A large no. of proteins not previously suspected of contg. amino acid sequences that bind SH3 domains are shown to contain such sequences.

IC ICM A61K038-10
ICS C07K007-08
NCL 514013000
CC 6-3 (General Biochemistry)
Section cross-reference(s): 3, 7

IT Proteins, specific or class
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(**Immune** suppressor factor J6B7, SH3 domain identified in; SH3-binding peptides specific for the Src-family of proteins)

IT Androgen receptors
Calcitonin receptors
Calcium channel
Chloride channel
Cytokine receptors
Dystrophin
Epidermal growth factor receptors
Ezrin
Fas ligand
GTPase-activating protein
Insulin-like growth factor-binding proteins
Muscarinic receptors
Myosins
Potassium channel
Progesterone receptors
Retinoic acid receptors
Ryanodine receptors
Sodium channel
neu (receptor)
p53 (protein)
RL: BOC (Biological occurrence); BSU (Biological study, unclassified);

BIOL (Biological study); OCCU (Occurrence)
(SH3 domain identified in; SH3-binding peptides specific for the Src-family of proteins)
REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 10 OF 26 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:813365 HCAPLUS
DOCUMENT NUMBER: 134:98367
TITLE: Distribution of proteins implicated in excitation-contraction coupling in rat ventricular myocytes
AUTHOR(S): Scriven, David R. L.; Dan, Pauline; Moore, Edwin D. W.
CORPORATE SOURCE: Department of Physiology, University of British Columbia, Vancouver, BC, V6T 1Z3, Can.
SOURCE: Biophysical Journal (2000), 79(5), 2682-2691
CODEN: BIOJAU; ISSN: 0006-3495
PUBLISHER: Biophysical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We have examd. the distribution of ryanodine receptors, L-type Ca2+ channels, calsequestrin, Na+/Ca2+ exchangers, and voltage-gated Na+ channels in adult rat ventricular myocytes. Enzymically dissocd. cells were fixed and dual-labeled with specific antibodies using std. immunocytochem. protocols. Images were deconvolved to reverse the optical distortion produced by wide-field microscopes equipped with high numerical aperture objectives. Every image showed a well-ordered array of fluorescent spots, indicating that all of the proteins examd. were distributed in discrete clusters throughout the cell. Math. anal. of the images revealed that dyads contained only ryanodine receptors, L-type Ca2+ channels, and calsequestrin, and excluded Na+/Ca2+ exchangers and voltage-gated Na+ channels. The Na+/Ca2+ exchanger and voltage-gated Na+ channels were distributed largely within the t-tubules, on both transverse and axial elements, but were not co-localized. The t-tubule can therefore be subdivided into at least three structural domains; one of coupling (dyads), one contg. the Na+/Ca2+ exchanger, and one contg. voltage-gated Na+ channels. We conclude that if either the slip mode conductance of the Na+ channel or the reverse mode of the Na+/Ca2+ exchanger are to contribute to the contractile force, the fuzzy space must extend outside of the dyad.
CC 13-1 (Mammalian Biochemistry)
IT **Calcium channel**
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(L-type; **immunofluorescence** and microscopic studies of distribution of **calcium** and sodium **channels**, **ryanodine receptors** and calsequestrins in rat ventricular myocytes)
IT Organelle
(T-tubule system; **immunofluorescence** and microscopic studies of distribution of **calcium** and sodium **channels**, **ryanodine receptors** and calsequestrins in rat ventricular myocytes)
IT Transport proteins
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(**calcium**-sodium-exchanging; **immunofluorescence** and microscopic studies of distribution of **calcium** and sodium **channels**, **ryanodine receptors** and calsequestrins in rat ventricular myocytes)

IT Calsequestrin
Ryanodine receptors
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(**immunofluorescence** and microscopic studies of distribution of **calcium** and sodium **channels**, **ryanodine receptors** and calsequestrins in rat ventricular myocytes)
IT Heart
(ventricle, myocyte; **immunofluorescence** and microscopic studies of distribution of **calcium** and sodium **channels**, **ryanodine receptors** and calsequestrins in rat ventricular myocytes)
IT Sodium **channel**
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(voltage-gated; **immunofluorescence** and microscopic studies of distribution of **calcium** and sodium **channels**, **ryanodine receptors** and calsequestrins in rat ventricular myocytes)
REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 11 OF 26 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:605386 HCAPLUS
DOCUMENT NUMBER: 133:319862
TITLE: Calmodulin and **immunophilin** are required as functional partners of a **ryanodine receptor** in ascidian oocytes at fertilization
AUTHOR(S): Albrieux, Mireille; Moutin, Marie-Jo; Grunwald, Didier; Villaz, Michel
CORPORATE SOURCE: Laboratoire Canaux Ioniques et Signalisation, Departement de Biologie Moleculaire et Structurale, INSERM E 9931, Grenoble, F-38054, Fr.
SOURCE: Developmental Biology (2000), 225(1), 101-111
CODEN: DEBIAO; ISSN: 0012-1606
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Fertilization of oocytes incites numerous changes relying on Ca2+ signaling. In inseminated ascidian eggs, an increase in the egg surface membrane, monitored by a change in elec. capacitance, is recorded at the onset of meiosis resumption. This membrane addn. to the cell surface is controlled by calcium release through a ryanodine receptor (RyR), sensitive to cyclic ADP-ribose. Using confocal microscopy anal. of ascidian oocytes immunostained with anti-RyR antibody, we show here that this calcium channel is asym. located in the vegetal cortical zone. Interestingly, the increase in cell capacitance occurring at fertilization is correlated with a fluorescent signal, imaged by the marker of vesicle trafficking FM 1-43, located close to the RyR region. Two putative partners of RyR, namely an FKBP-like protein and a calmodulin, are identified in these oocyte exts. by detection of enzyme activity and PCR amplification. Both are necessary to sustain ryanodine receptor activity in these oocytes since the membrane insertion triggered by fertilization is inhibited by the FKBP ligand rapamycin and by a calmodulin antagonist peptide. These findings suggest that exocytosis in ascidian eggs is triggered at fertilization by a functional Ca2+ release unit operating as a complex of several proteins, including a calmodulin and an immunophilin, around the intracellular calcium channel itself. (c) 2000 Academic Press.
CC 12-6 (Nonmammalian Biochemistry)
ST **ryanodine receptor** egg Phallusia calmodulin

immunophilin

IT Biological transport
(**calcium**; calmodulin and **immunophilin** are functional partners of **ryanodine receptor** in ascidian oocytes at fertilization)

IT Exocytosis
Fertilization
Phallusia mamillata
(calmodulin and **immunophilin** are functional partners of **ryanodine receptor** in ascidian oocytes at fertilization)

IT **Calcium channel**
Calmodulins
Immunophilins
Ryanodine receptors
RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(calmodulin and **immunophilin** are functional partners of **ryanodine receptor** in ascidian oocytes at fertilization)

IT Egg
(oocyte; calmodulin and **immunophilin** are functional partners of **ryanodine receptor** in ascidian oocytes at fertilization)

IT **7440-70-2**, **Calcium**, biological studies
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(calmodulin and **immunophilin** are functional partners of **ryanodine receptor** in ascidian oocytes at fertilization)

REFERENCE COUNT: 63 THERE ARE 63 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 12 OF 26 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:795994 HCAPLUS
DOCUMENT NUMBER: 132:31744
TITLE: Gene probes used for genetic profiling in healthcare screening and planning
INVENTOR(S): Roberts, Gareth Wyn
PATENT ASSIGNEE(S): Genostic Pharma Ltd., UK
SOURCE: PCT Int. Appl., 745 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9964627	A2	19991216	WO 1999-GB1780	19990604

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG,

CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.:
GB 1998-12099 A 19980606
GB 1998-13291 A 19980620
GB 1998-13611 A 19980624
GB 1998-13835 A 19980627
GB 1998-14110 A 19980701
GB 1998-14580 A 19980707
GB 1998-15438 A 19980716
GB 1998-15574 A 19980718
GB 1998-15576 A 19980718
GB 1998-16085 A 19980724
GB 1998-16086 A 19980724
GB 1998-16921 A 19980805
GB 1998-17097 A 19980807
GB 1998-17200 A 19980808
GB 1998-17632 A 19980814
GB 1998-17943 A 19980819

AB There is considerable evidence that significant factor underlying the individual variability in response to disease, therapy and prognosis lies in a person's genetic make-up. There have been numerous examples relating that polymorphisms within a given gene can alter the functionality of the protein encoded by that gene thus leading to a variable physiol. response. In order to bring about the integration of genomics into medical practice and enable design and building of a technol. platform which will enable the everyday practice of mol. medicine a way must be invented for the DNA sequence data to be aligned with the identification of genes central to the induction, development, progression and outcome of disease or physiol. states of interest. According to the invention, the no. of genes and their configurations (mutations and polymorphisms) needed to be identified in order to provide crit. clin. information concerning individual prognosis is considerably less than the 100,000 thought to comprise the human genome. The identification of the identity of the core group of genes enables the invention of a design for genetic profiling technologies which comprises of the identification of the core group of genes and their sequence variants required to provide a broad base of clin. prognostic information - "genostics". The "Genostic" profiling of patients and persons will radically enhance the ability of clinicians, healthcare professionals and other parties to plan and manage healthcare provision and the targeting of appropriate healthcare resources to those deemed most in need. The use of this invention could also lead to a host of new applications for such profiling technologies, such as identification of persons with particular work or environment related risk, selection of applicants for employment, training or specific opportunities or for the enhancing of the planning and organization of health services, education services and social services.

IC ICM C12Q001-68
ICS C07K016-18
CC 3-1 (Biochemical Genetics)
Section cross-reference(s): 9, 13, 14

IT Chromogranins
Cyclins
Glycophorins
Immunoglobulins
RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(A, core group of disease-related genes; gene probes used for genetic profiling in healthcare screening and planning)

IT **Adenosine** receptors
RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)

(A2, core group of disease-related genes; gene probes used for genetic profiling in healthcare screening and planning)

IT **Antigens**
RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(**CD135**, core group of disease-related genes; gene probes used for genetic profiling in healthcare screening and planning)

IT **Antigens**
RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(CD90, core group of disease-related genes; gene probes used for genetic profiling in healthcare screening and planning)

IT Apolipoproteins
Cyclins
Immunoglobulins
RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(D, core group of disease-related genes; gene probes used for genetic profiling in healthcare screening and planning)

IT **Gene, animal**
RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(DSS1, core group of disease-related genes; gene probes used for genetic profiling in healthcare screening and planning)

IT **Dopamine receptors**
RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(D1, core group of disease-related genes; gene probes used for genetic profiling in healthcare screening and planning)

IT Apolipoproteins
Immunoglobulins
RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(E, core group of disease-related genes; gene probes used for genetic profiling in healthcare screening and planning)

IT **Immunoglobulins**
RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(G2, core group of disease-related genes; gene probes used for genetic profiling in healthcare screening and planning)

IT **Immunoglobulin** receptors
RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(IgE type II, core group of disease-related genes; gene probes used for genetic profiling in healthcare screening and planning)

IT **Immunoglobulin** receptors
RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(IgG type I, core group of disease-related genes; gene probes used for genetic profiling in healthcare screening and planning)

IT **Immunoglobulin** receptors
RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(IgG type IIA, core group of disease-related genes; gene probes used for genetic profiling in healthcare screening and planning)

IT **Immunoglobulins**
RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(J protein, core group of disease-related genes; gene probes used for genetic profiling in healthcare screening and planning)

IT **Immunoglobulins**
Laminins
RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(M, core group of disease-related genes; gene probes used for genetic profiling in healthcare screening and planning)
IT Receptors
RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(**calcium**, core group of disease-related genes; gene probes used for genetic profiling in healthcare screening and planning)
IT Transport proteins
RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(**calcium**-sodium-exchanging, core group of disease-related genes; gene probes used for genetic profiling in healthcare screening and planning)
IT ACTH receptors
Albumins, biological studies
Amelogenins
Amyloid precursor proteins
Androgen receptors
Aromatic hydrocarbon receptors
Arrestins
Benzodiazepine receptors
CD1 (antigen)
CD14 (antigen)
CD19 (antigen)
CD2 (antigen)
CD20 (antigen)
CD22 (antigen)
CD26 (antigen)
CD28 (antigen)
CD3 (antigen)
CD34 (antigen)
CD36 (antigen)
CD38 (antigen)
CD4 (antigen)
CD40 (antigen)
CD44 (antigen)
CD45 (antigen)
CD5 (antigen)
CD59 (antigen)
CD68 (antigen)
CD69 (antigen)
CD7 (antigen)
CD8 (antigen)
CD80 (antigen)
CD86 (antigen)
CFTR (cystic fibrosis transmembrane conductance regulator)
CTLA-4 (antigen)
Calcitonin gene-related peptide receptors
Calcitonin receptors
Calnexin
Calretinin
Cannabinoid receptors
Carcinoembryonic antigen
Cell adhesion molecules
Ciliary neurotrophic factor
Clathrin

Clusterin
Corticosteroid receptors
Corticotropin releasing factor receptors
Cyclophilins
Desmins
Dynamin
Dyneins
Dystrophin
Elastins
Epidermal growth factor receptors
Erythropoietin receptors
FSH receptors
Fas antigen
Ferritins
Fibrinogens
Fibronectins
GTPase-activating protein
Galanin receptors
Gastrin-releasing peptide receptors
Gelsolin
Glucagon receptors
Glucagon-like peptide-1 receptors
Glucocorticoid receptors
Gonadotropin receptors
Gonadotropin-releasing hormone receptor
Growth factor receptors
Growth hormone receptors
Growth hormone-releasing hormone receptors
Hemoglobins
Hemopexins
Hepatocyte growth factor
Heregulins
Immunoglobulin receptors
Insulin receptors
Insulin-like growth factor I receptors
Insulin-like growth factor II receptors
Interleukin 1 receptor antagonist
Interleukin 1 receptors
Interleukin 10
Interleukin 11
Interleukin 13
Interleukin 1.alpha.
Interleukin 1.beta.
Interleukin 3
Interleukin 3 receptors
Interleukin 4
Interleukin 4 receptors
Interleukin 5
Interleukin 5 receptors
Interleukin 6
Interleukin 6 receptors
Interleukin 7
Interleukin 7 receptors
Interleukin 8
Interleukin 8 receptors
Interleukin 9
Intrinsic factors
Invariant chain (class II antigen)
LFA-3 (antigen)
Lactoferrins

Leptin receptors
Leukemia inhibitory factor
Leukemia inhibitory factor receptors
Leukosialin
Lymphotoxin
Macrophage colony-stimulating factor receptors
Macrophage inflammatory protein 2
Metallothioneins
Mineralocorticoid receptors
Moesins
Monocyte chemoattractant protein-1
Multidrug resistance proteins
Myelin P0 protein
Myelin basic protein
Myoglobins
Nerve growth factor receptors
Neurotensin receptors
Nicotinic receptors
Opioid receptors
Osteocalcins
Osteonectin
Osteopontin
Oxytocin receptors
Parathyroid hormone receptors
Parvalbumins
Pituitary adenylate cyclase-activating polypeptide receptor
Platelet-activating factor receptors
Platelet-derived growth factor receptors
Platelet-derived growth factors
Prion proteins
Progesterone receptors
Prolactin receptors
Proliferating cell nuclear antigen
Prostanoid receptors
Proteolipid protein
Radixin
Ras proteins
Rhodopsins
Ryanodine receptors
Secretin receptors
Stem cell factor
Sulfonylurea receptors
Synaptophysin
TCR .alpha..beta. (receptor)
Talin
Tau factor
Tenascins
Thrombin receptors
Thrombomodulin
Thrombospondins
Thromboxane receptors
Thyroglobulin
Thyrotropin receptors
Thyrotropin-releasing hormone receptors
Titins
Transcortins
Transferrin receptors
Transferrins
Transthyretin
Tubulins

Tumor necrosis factor receptors
Tumor necrosis factors
Urokinase-type plasminogen activator receptors
VIP receptors
Vasopressin receptors
Villin
Vimentins
Vinculin
Vitamin D receptors
neu (receptor)
p53 (protein)
.alpha.-Fetoproteins
.alpha.1-Acid glycoprotein
RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(core group of disease-related genes; gene probes used for genetic profiling in healthcare screening and planning)

IT Behavior
Development, mammalian postnatal
Immunity
Metabolism, animal
Sexual behavior
(disorder, core group of disease-related genes; gene probes used for genetic profiling in healthcare screening and planning)

L18 ANSWER 13 OF 26 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:795993 HCAPLUS
DOCUMENT NUMBER: 132:31743
TITLE: Gene probes used for genetic profiling in healthcare screening and planning
INVENTOR(S): Roberts, Gareth Wyn
PATENT ASSIGNEE(S): Genostic Pharma Limited, UK
SOURCE: PCT Int. Appl., 149 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9964626	A2	19991216	WO 1999-GB1779	19990604
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9941586	A1	19991230	AU 1999-41586	19990604
AU 9941587	A1	19991230	AU 1999-41587	19990604
GB 2339200	A1	20000119	GB 1999-12914	19990604
GB 2339200	B2	20010912		
EP 1084273	A1	20010321	EP 1999-925207	19990604
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

PRIORITY APPLN. INFO.: GB 1998-12098 A 19980606
GB 1998-28289 A 19981223

GB	1998-16086	A	19980724
GB	1998-16921	A	19980805
GB	1998-17097	A	19980807
GB	1998-17200	A	19980808
GB	1998-17632	A	19980814
GB	1998-17943	A	19980819
WO	1999-GB1779	W	19990604

AB There is considerable evidence that significant factor underlying the individual variability in response to disease, therapy and prognosis lies in a person's genetic make-up. There have been numerous examples relating that polymorphisms within a given gene can alter the functionality of the protein encoded by that gene thus leading to a variable physiol. response. In order to bring about the integration of genomics into medical practice and enable design and building of a technol. platform which will enable the everyday practice of mol. medicine a way must be invented for the DNA sequence data to be aligned with the identification of genes central to the induction, development, progression and outcome of disease or physiol. states of interest. According to the invention, the no. of genes and their configurations (mutations and polymorphisms) needed to be identified in order to provide crit. clin. information concerning individual prognosis is considerably less than the 100,000 thought to comprise the human genome. The identification of the identity of the core group of genes enables the invention of a design for genetic profiling technologies.

IC ICM C12Q001-68
ICS C07K016-18

CC 3-1 (Biochemical Genetics)
Section cross-reference(s): 9, 13, 14

IT Bone morphogenetic proteins
Keratins
RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(8, core group of disease-related genes; gene probes used for genetic profiling in healthcare screening and planning)

IT Chromogranins
Cyclins
Glycophorins
Immunoglobulins
RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(A, core group of disease-related genes; gene probes used for genetic profiling in healthcare screening and planning)

IT **Antigens**
RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(**CD116**, core group of disease-related genes; gene probes used for genetic profiling in healthcare screening and planning)

IT **CD** antigens
RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(CD57, core group of disease-related genes; gene probes used for genetic profiling in healthcare screening and planning)

IT **Gene, animal**
RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(CYP4F3, core group of disease-related genes; gene probes used for genetic profiling in healthcare screening and planning)

IT **Gene, animal**
RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)

(CYP5A1, core group of disease-related genes; gene probes used for genetic profiling in healthcare screening and planning)

IT Apolipoproteins
Cyclins
Immunoglobulins
RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(D, core group of disease-related genes; gene probes used for genetic profiling in healthcare screening and planning)

IT Apolipoproteins
Immunoglobulins
RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(E, core group of disease-related genes; gene probes used for genetic profiling in healthcare screening and planning)

IT **Immunoglobulins**
RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(G2, core group of disease-related genes; gene probes used for genetic profiling in healthcare screening and planning)

IT **Immunoglobulin** receptors
RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(IgE type II, core group of disease-related genes; gene probes used for genetic profiling in healthcare screening and planning)

IT **Immunoglobulin** receptors
RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(IgG type I, core group of disease-related genes; gene probes used for genetic profiling in healthcare screening and planning)

IT **Immunoglobulin** receptors
RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(IgG type IIA, core group of disease-related genes; gene probes used for genetic profiling in healthcare screening and planning)

IT **Immunoglobulins**
RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(J protein, core group of disease-related genes; gene probes used for genetic profiling in healthcare screening and planning)

IT **Immunoglobulins**
Laminins
RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(M, core group of disease-related genes; gene probes used for genetic profiling in healthcare screening and planning)

IT Receptors
RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(**calcium**, core group of disease-related genes; gene probes used for genetic profiling in healthcare screening and planning)

IT Transport proteins
RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(**calcium**-sodium-exchanging, core group of disease-related genes; gene probes used for genetic profiling in healthcare screening and planning)

IT ACTH receptors
Albumins, biological studies
Amelogenins

Amyloid precursor proteins
Androgen receptors
Aromatic hydrocarbon receptors
Arrestins
Benzodiazepine receptors
CD1 (antigen)
CD14 (antigen)
CD19 (antigen)
CD2 (antigen)
CD20 (antigen)
CD22 (antigen)
CD26 (antigen)
CD28 (antigen)
CD3 (antigen)
CD34 (antigen)
CD36 (antigen)
CD38 (antigen)
CD4 (antigen)
CD40 (antigen)
CD44 (antigen)
CD45 (antigen)
CD5 (antigen)
CD59 (antigen)
CD68 (antigen)
CD69 (antigen)
CD7 (antigen)
CD8 (antigen)
CD80 (antigen)
CD86 (antigen)
CFTR (cystic fibrosis transmembrane conductance regulator)
CTLA-4 (antigen)
Calcitonin gene-related peptide receptors
Calcitonin receptors
Calnexin
Calretinin
Cannabinoid receptors
Carcinoembryonic antigen
Cell adhesion molecules
Ciliary neurotrophic factor
Clathrin
Clusterin
Corticosteroid receptors
Corticotropin releasing factor receptors
Cyclophilins
Desmins
Dynamin
Dyneins
Dystrophin
Elastins
Epidermal growth factor receptors
Erythropoietin receptors
FSH receptors
Fas antigen
Ferritins
Fibrinogens
Fibronectins
GTPase-activating protein
Galanin receptors
Gastrin-releasing peptide receptors
Gelsolin

Glucagon receptors
Glucagon-like peptide-1 receptors
Glucocorticoid receptors
Gonadotropin receptors
Gonadotropin-releasing hormone receptor
Growth factor receptors
Growth hormone receptors
Growth hormone-releasing hormone receptors
Hemoglobins
Hemopexins
Hepatocyte growth factor
Heregulins
Immunoglobulin receptors
Insulin receptors
Insulin-like growth factor I receptors
Insulin-like growth factor II receptors
Interleukin 1 receptor antagonist
Interleukin 1 receptors
Interleukin 10
Interleukin 11
Interleukin 13
Interleukin 1.alpha.
Interleukin 1.beta.
Interleukin 3
Interleukin 3 receptors
Interleukin 4
Interleukin 4 receptors
Interleukin 5
Interleukin 5 receptors
Interleukin 6
Interleukin 6 receptors
Interleukin 7
Interleukin 7 receptors
Interleukin 8
Interleukin 8 receptors
Interleukin 9
Intrinsic factors
Invariant chain (class II antigen)
LFA-3 (antigen)
Lactoferrins
Leptin receptors
Leukemia inhibitory factor
Leukemia inhibitory factor receptors
Leukosialin
Lymphotoxin
Macrophage colony-stimulating factor receptors
Macrophage inflammatory protein 2
Metallothioneins
Mineralocorticoid receptors
Moesins
Monocyte chemoattractant protein-1
Multidrug resistance proteins
Myelin P0 protein
Myelin basic protein
Myoglobins
Nerve growth factor receptors
Neurotensin receptors
Nicotinic receptors
Opioid receptors
Osteocalcins

Osteonectin
Osteopontin
Oxytocin receptors
Parathyroid hormone receptors
Parvalbumins
Pituitary adenylate cyclase-activating polypeptide receptor
Platelet-activating factor receptors
Platelet-derived growth factor receptors
Platelet-derived growth factors
Prion proteins
Progesterone receptors
Prolactin receptors
Proliferating cell nuclear antigen
Prostanoid receptors
Proteolipid protein
Radixin
Ras proteins
Rhodopsins
Ryanodine receptors
Secretin receptors
Stem cell factor
Sulfonylurea receptors
Synaptophysin
TCR .alpha..beta. (receptor)
Talin
Tau factor
Tenascins
Thrombin receptors
Thrombomodulin
Thrombospondins
Thromboxane receptors
Thyroglobulin
Thyrotropin receptors
Thyrotropin-releasing hormone receptors
Titins
Transcortins
Transferrin receptors
Transferrins
Transthyretin
Tubulins
Tumor necrosis factor receptors
Tumor necrosis factors
Urokinase-type plasminogen activator receptors
VIP receptors
Vasopressin receptors
Villin
Vimentins
Vinculin
Vitamin D receptors
neu (receptor)
p53 (protein)
.alpha.-Fetoproteins
.alpha.1-Acid glycoprotein
RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(core group of disease-related genes; gene probes used for genetic profiling in healthcare screening and planning)

L18 ANSWER 14 OF 26 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:222503 HCAPLUS

DOCUMENT NUMBER: 131:13605
TITLE: Cyclosporin A treatment alters characteristics of Ca2+-release channel in cardiac sarcoplasmic reticulum
AUTHOR(S): Park, Kyoung Sik; Kim, Tae Kon; Kim, Do Han
CORPORATE SOURCE: Department of Life Science, Kwangju Institute of Science and Technology, Kwangju, 500-712, S. Korea
SOURCE: American Journal of Physiology (1999), 276(3, Pt. 2), H865-H872
CODEN: AJPHAP; ISSN: 0002-9513
PUBLISHER: American Physiological Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Chronic treatment with cyclosporin A (CsA) has been reported to induce reversible alterations of contractile properties in rat hearts. To define the mol. mechanisms underlying the physiol. alterations, the Ca2+-release channel (CRC) and Ca2+-ATPase from sarcoplasmic reticulum in rats were examd. Ryanodine binding to whole homogenates of rat hearts shows time- and dose-dependent alterations in CRC properties by CsA. On 3 wk of treatment with 15 mg CsA kg body wt-1 day-1, 1) maximal ryanodine binding (Bmax) decreased, 2) the dissocn. const. of ryanodine (Kd increased, 3) caffeine sensitivity of CRC increased, and 4) ruthenium red sensitivity of CRC decreased. On the other hand, Bm,, and Kd of ryanodine binding in rat skeletal muscles were not changed. Ryanodine-sensitive oxalate-supported Ca2+ uptake in whole homogenates was lower in CsA-treated rat hearts than in control hearts, whereas total Ca2+ uptake in the presence of 500 M ryanodine was not changed. Functional expts. with rapamycin and Western blot anal. suggest that the CsA-induced alteration of ryanodine binding is due at least in part to an upregulation of calcineurin. The heart muscle-specific alterations of CRC could be responsible for the previously reported contractile changes of CsA-treated rat hearts.

CC 1-7 (Pharmacology)

ST heart **calcium** release **channel** cyclosporine cardiotoxicity; cyclosporin A cardiac sarcoplasmic reticulum **ryanodine receptor calcium**

IT **Calcium channel**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**calcium**-release **channel**; cyclosporin A treatment alters characteristics of Ca2+-release **channel** in cardiac sarcoplasmic reticulum)

IT Heart
Immunosuppressants
(cyclosporin A treatment alters characteristics of Ca2+-release channel in cardiac sarcoplasmic reticulum)

IT **Ryanodine receptors**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(cyclosporin A treatment alters characteristics of Ca2+-release channel in cardiac sarcoplasmic reticulum)

IT 9000-83-3, ATPase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**calcium**-dependent; cyclosporin A treatment alters characteristics of Ca2+-release **channel** in cardiac sarcoplasmic reticulum)

REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 15 OF 26 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:804256 HCAPLUS

DOCUMENT NUMBER: 130:48489
TITLE: Common **immunophilin** mechanism for noncoplanar PCBs and naturally occurring bromotyrosines from Ianthella basta
AUTHOR(S): Pessah, Isaac N.
CORPORATE SOURCE: Department Molecular Biosciences, School Veterinary Medicine, University California, Davis, CA, 95616, USA
SOURCE: Organohalogen Compounds (1998), 37(Toxicology, Endocrine Disruption, Metabolism and Kinetics), 13-17
CODEN: ORCOEP; ISSN: 1026-4892
PUBLISHER: ECO-INFORMA Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The mol. mechanism was investigated by which noncoplanar polychlorinated biphenyls (PCBs) alter Ca2+ regulation at the level of single channels and disrupt Ca2+ signaling in intact cells. Bastadins were extd. from I. basta and their structures were elucidated by NMR and mass spectral analyses. Electrophysiol. studies were carried out in planar lipid bilayer (BLM) expts. and the mechanisms of noncoplanar PCBs and bastadins were studied in PC12 cells. Bastadin 10 dramatically relieved the dependence of channel activation on Ca2+ in the physiol. concn. range in both radioligand receptor binding and single channel expts. The actions of bastadin 10 on microsomal Ca2+ efflux and channel open time were completely and selectively eliminated by the immunosuppressant FK506, implying the actions of bastadin 10 are mediated by FK-506-binding protein (FKBP)12. SR pretreated with FK506 effectively removed FKBP1 from RyR receptor. Ratio fluorescence imaging revealed that PCB95 altered Ca2+-signaling in PC12 cells. These actions were eliminated by pretreatment with FK506 or rapamycin or RyR blockers. These results show that ortho-substituted PCBs alter microsomal Ca2+ transport by a receptor-mediated mechanism involving the major T-cell immunophilin FKBP12.

CC 4-3 (Toxicology)
ST bastadin 10 Ianthella **calcium channel** FKBP12; PCB noncoplanar **calcium channel** FKBP12
IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(FKBP-12 (FK 506-binding protein, 12,000-mol.-wt.); FK506 effect on FKBP12 eliminating noncoplanar PCBs and bastadin 10 action on **Ca channel**)
IT **Calcium channel**
Ryanodine receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(coplanar PCBs and bastadin 10 from Ianthella basta effects on Ca2+ regulation at single **channel** level)
IT **Immunophilins**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(**immunophilin** mechanism for noncoplanar PCBs and naturally occurring bastadin 10 from Ianthella basta)
IT 104987-11-3, FK506
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(FK506 effect on **immunophilins** eliminating noncoplanar PCBs and bastadin 10 action on **Ca channel**)
IT 127687-08-5, Bastadin 10
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

(**immunophilin** mechanism for noncoplanar PCBs and naturally occurring bastadin 10 from Ianthella basta)
REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 16 OF 26 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:411041 HCAPLUS
DOCUMENT NUMBER: 127:46047
TITLE: Detection of gene mutation in patients with idiopathic dilated cardiomyopathy
INVENTOR(S): Sen, Luyi; Philipson, Kenneth D.; Lusis, Aldons Jake
PATENT ASSIGNEE(S): University of California, USA
SOURCE: U.S., 23 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5639614	A	19970617	US 1995-480481	19950607

AB A genetic mutation within the SR calcium release channel provides a test for susceptibility to idiopathic dilated cardiomyopathy. The mutation(s) was found to comprise .G.fwdarw.A and/or G.fwdarw.T substitutions at positions 380 and 776 within a DNA fragment encoding a portion of the sarcoplasmic reticulum calcium release channel protein. These mutations are consistently assocd. with idiopathic dilated cardiomyopathy and ischemic cardiomyopathy. The test detects the presence of the mutation(s) in a sample of nucleic acids obtained from the individual being tested. Restriction fragment length polymorphism is one technique which can be used in the test. Thus, PCR primers are designed to amplify a portion of the calcium release channel gene contg. these mutations, and HindIII restriction endonuclease used to provide a 3.7-kb RFLP fragment indicative of the disease condition. An immunohistochem. test for idiopathic dilated cardiomyopathy is also described. A method for drug discovery is provided using the mutant calcium channel protein.
IC ICM C12Q001-68
ICS C07H021-04; C12P019-34
NCL 435006000
CC 3-1 (Biochemical Genetics)
Section cross-reference(s): 9, 14
ST idiopathic dilated cardiomyopathy gene mutation detection; PCR gene mutation idiopathic dilated cardiomyopathy; RFLP gene mutation idiopathic dilated cardiomyopathy; **calcium channel** mutation idiopathic dilated cardiomyopathy
IT **Calcium channel**
Ryanodine receptors
RL: ADV (Adverse effect, including toxicity); ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(detection of gene mutation in humans with idiopathic dilated cardiomyopathy)
IT **Immunoassay**
(**immunohistochem.**; detection of gene mutation in humans with idiopathic dilated cardiomyopathy)
IT DNA sequences
(of **calcium** release **channel** gene mutation in humans with idiopathic dilated cardiomyopathy)
IT Protein sequences

(of **calcium** release **channel** mutation in humans with idiopathic dilated cardiomyopathy)

L18 ANSWER 17 OF 26 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:301895 HCAPLUS
DOCUMENT NUMBER: 127:15793
TITLE: The **immunophilin** FK506-binding protein modulates Ca2+ release channel closure in rat heart
AUTHOR(S): Xiao, Rui-Ping; Valdivia, Hector H.; Bogdanov, Konstantin; Valdivia, Carmen; Lakatta, Edward G.; Cheng, Heping
CORPORATE SOURCE: Laboratory of Cardiovascular Science, Gerontology Research Center, National Institute on Aging, National Institutes of Health, Baltimore, MD, 21224, USA
SOURCE: Journal of Physiology (Cambridge, United Kingdom) (1997), 500(2), 343-354
CODEN: JPHYA7; ISSN: 0022-3751
PUBLISHER: Cambridge University Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The nature of the signal that terminates the release of Ca2+ from the cardiac sarcoplasmic reticulum has remained elusive. This study was intended to examine whether FK506-binding protein (FKBP), which is tightly assocd. to the ryanodine receptor (RyR)/Ca2+ release channel, plays a role in the termination of Ca2+-induced Ca2+ release (CICR) in heart. Confocal microscopy and the Ca2+ indicator fluo-3 were used to visualize the elementary release events, i.e. "Ca2+ sparks" in rat ventricular myocytes under resting or voltage-clamped conditions. Addnl., electrophysiol. single-channel recordings, at const. [Ca2+] or during [Ca2+] steps produced by photorelease of caged Ca2+, were obtained from rat cardiac RyRs incorporated in planar lipid bilayers. Inhibition of FKBP by the immunosuppressants FK506 or rapamycin increased the duration of spontaneous or depolarization-evoked Ca2+ sparks 6- to 7-fold. In addn., Ca2+ sparks were seen with two-level amplitudes, corresponding to full and half normal spark amplitude. 4. FK506 potentiated and prolonged elec. stimulated [Ca2+]i transients and contractions, but did not affect the amplitude and kinetics of the L-type Ca2+ channel current. In planar lipid bilayers, FK506 (15 .mu.M) prolonged .apprx.7-fold the mean open lifetime of reconstituted single RyRs, induced the appearance of long-lasting subconductance states, and markedly showed the spontaneous decay of RyR activity elicited by fast and sustained Ca2+ stimuli. The time const. of the spontaneous decay of activity increased from 1.8 s in control to .gtoreq. 20 s in the presence of FK506. We conclude that FKBP may afford an intrinsic mechanism to terminate RyR openings and it may thus exert a neg. feedback on CICR in heart cells.

CC 13-2 (Mammalian Biochemistry)
Section cross-reference(s): 1
ST FKBP protein **calcium** release **channel** heart; **ryanodine receptor** FK506 rapamycin **calcium** release
IT Proteins, specific or class
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(FKBP (FK 506-binding protein); **immunophilin** FK506-binding protein modulates Ca2+ release channel closure in rat heart)
IT **Calcium channel**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**calcium**-release **channel**; **immunophilin**

FK506-binding protein modulates Ca2+ release **channel** closure in rat heart)

IT Cardiac contraction
Heart
Immunosuppressants
(**immunophilin** FK506-binding protein modulates Ca2+ release channel closure in rat heart)

IT **Ryanodine receptors**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**immunophilin** FK506-binding protein modulates Ca2+ release channel closure in rat heart)

IT Heart
(myocyte; **immunophilin** FK506-binding protein modulates Ca2+ release channel closure in rat heart)

IT 104987-11-3, FK506
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(**immunophilin** FK506-binding protein modulates Ca2+ release channel closure in rat heart)

IT **7440-70-2, Calcium**, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**immunophilin** FK506-binding protein modulates Ca2+ release **channel** closure in rat heart)

IT 53123-88-9, Rapamycin
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(**immunophilin** FK506-binding protein modulates Ca2+ release channel closure in rat heart in relation to)

IT **7440-70-2, Calcium**, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(transport; **immunophilin** FK506-binding protein modulates Ca2+ release **channel** closure in rat heart)

L18 ANSWER 18 OF 26 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1996:325752 HCAPLUS
DOCUMENT NUMBER: 125:25848
TITLE: Effects of rapamycin on **ryanodine receptor**/Ca2+-release channels from cardiac muscle
AUTHOR(S): Kaftan, Edward; Marks, Andrew R.; Ehrlich, Barbara E.
CORPORATE SOURCE: Departments Physiology Medicine, University Connecticut, Farmington, CT, USA
SOURCE: Circulation Research (1996), 78(6), 990-997
CODEN: CIRUAL; ISSN: 0009-7330
PUBLISHER: American Heart Association
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Ryanodine receptors (RyRs) are intracellular channels that regulate the release of Ca2+ from the endoplasmic reticulum of many cell types. The RyRs are phys. assocd. with FK506-binding proteins (FKBPs); immunophilins, with cis-trans peptidyl-prolyl isomerase activity. FKBP12 copurifies with RyR1 (skeletal isoform) and modulates its gating. A different form of FKBP with a slightly higher mol. wt. copurifies with RyR2 (cardiac isoform). Previous studies have demonstrated that FKBP stabilizes gating of the skeletal Ca2+-release channel. In the present study, we measured the activity of cardiac RyRs incorporated into planar lipid bilayers to show that rapamycin, a drug that inhibits the prolyl isomerase activity of

FKBP and dissocs. FKBP from the RyR, increases the open probability and reduces the current amplitude of cardiac muscle Ca2+-release channels. These expts. show for the first time that submicromolar concns. of rapamycin can alter channel function. Our results provide support for the hypotheses that FKBP functionally assocs. with the RyR and that the immunosuppressant drug, rapamycin, alters the function of both cardiac and skeletal muscle isoforms of the Ca2+-release channel. Our findings suggest that FKBP-dependent modulation of channel function my be generally applicable to all members of the intracellular Ca2+-release channel family and that FKBPs may play important regulatory roles in many cell processes, ranging from long-term depression in neurons to contractility in cardiomyocytes.

CC 1-7 (Pharmacology)

ST rapamycin **ryanodine receptor calcium channel** heart; **immunosuppressant** rapamycin **ryanodine receptor calcium** heart

IT Heart
Immunosuppressants
(effects of rapamycin on **ryanodine receptor**/Ca2+-release channels from cardiac muscle)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(FKBP-12 (FK 506-binding protein, 12,000-mol.-wt.), effects of rapamycin on **ryanodine receptor**/Ca2+-release channels from cardiac muscle)

IT Ion **channel**
(**calcium**, effects of rapamycin on **ryanodine receptor**/Ca2+-release **channels** from cardiac muscle)

IT Biological transport
(efflux, effects of rapamycin on **ryanodine receptor**/Ca2+-release channels from cardiac muscle)

IT **Receptors**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**ryanodine**, effects of rapamycin on **ryanodine receptor**/Ca2+-release channels from cardiac muscle)

IT 53123-88-9, Rapamycin
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(effects of rapamycin on **ryanodine receptor**/Ca2+-release channels from cardiac muscle)

IT **7440-70-2**, **Calcium**, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(effects of rapamycin on **ryanodine receptor**/Ca2+-release **channels** from cardiac muscle)

L18 ANSWER 19 OF 26 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER:	1996:321487 HCAPLUS
DOCUMENT NUMBER:	125:6589
TITLE:	**Immunophilin** modulation of **calcium channel** gating
AUTHOR(S):	Marks, Andrew R.
CORPORATE SOURCE:	Cardiovascular Inst., Mount Sinai Sch Med., New York, NY, 10029, USA
SOURCE:	Methods (San Diego) (1996), 9(2), 177-187 CODEN: MTHDE9; ISSN: 1046-2023
PUBLISHER:	Academic
DOCUMENT TYPE:	Journal

LANGUAGE: English

AB The FK506 binding protein (FKBP12) is the cytosolic receptor for the immunosuppressant drugs FK506 and rapamycin. Recently, we have shown that FKBP12 copurifies with the ryanodine receptor (RyR), a 565,000-Da protein with four subunits that form the intracellular calcium release channels of the sarcoplasmic reticulum and endoplasmic reticulum. To identify the cellular function of FKBP12, in the absence of the ligands rapamycin and FK506, we coexpressed RyR and FKBP12 in insect cells. By measuring the single-channel properties of the RyR-FKBP complex reconstituted into planar lipid bilayers, we showed that FKBP12 modulates channel gating by decreasing channels with subconductance states, decreasing open probability after caffeine activation, and increasing mean open time. These effects were reversed by adding FK506 or rapamycin, both of which inhibit FKBP12 isomerase activity and dissoc. the FKBP-RyR complex. These studies provided a natural cellular (ligand-independent) function for FKBP12 and established that the functional calcium release channel complex includes FKBP12. We also expressed recombinant RyR1 in Xenopus laevis oocytes that lack FKBP12. Functional studies showed that the properties of the cloned RyR1, expressed in oocytes, were comparable to those of the native RyR1. These studies showed that FKBP12 is not required for tetrameric formation of the channel structure or for insertion into an intracellular calcium-contg. membrane. Both insect cells (Sf9) and Xenopus oocytes are excellent models for heterologous expression of FKBP12 and RyR. Combined with detn. of the single-channel properties of the resulting complex reconstituted into planar lipid bilayers, these approaches are well suited to the study of the role of FKBP12 as a modulator of calcium channel function.

CC 13-6 (Mammalian Biochemistry)
Section cross-reference(s): 6

ST **ryanodine receptor channel** gating FKBP12 protein; **calcium** release **channel** gating FKBP12 protein

IT Plasmid and Episome
(pB-SKRYR1 and pS-SKRYR1; role of FKBP12 protein in modulation of **ryanodine receptor calcium** release **channel** function studied by heterologous expression in Sf9 insect cells and Xenopus oocytes)

IT Proteins, specific or class
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(FKBP-12 (FK 506-binding protein, 12,000-mol.-wt.), role of FKBP12 protein in modulation of **ryanodine receptor calcium** release **channel** function studied by heterologous expression in Sf9 insect cells and Xenopus oocytes)

IT Ion **channel**
(**calcium**, role of FKBP12 protein in modulation of **ryanodine receptor calcium** release **channel** function studied by heterologous expression in Sf9 insect cells and Xenopus oocytes)

IT Ion **channel**
(**calcium**-release, role of FKBP12 protein in modulation of **ryanodine receptor calcium** release **channel** function studied by heterologous expression in Sf9 insect cells and Xenopus oocytes)

IT Biological transport
(**channel**-mediated, role of FKBP12 protein in modulation of **ryanodine receptor calcium** release **channel** function studied by heterologous expression in Sf9 insect cells and Xenopus oocytes)

IT **Receptors**

RL: BAC (Biological activity or effector, except adverse); BPN (Biosynthetic preparation); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PREP (Preparation); PROC (Process)
(**ryanodine**, role of FKBP12 protein in modulation of **ryanodine receptor calcium** release **channel** function studied by heterologous expression in Sf9 insect cells and Xenopus oocytes)

IT 15662-33-6, **Ryanodine**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**receptor**; role of FKBP12 protein in modulation of **ryanodine receptor calcium** release **channel** function studied by heterologous expression in Sf9 insect cells and Xenopus oocytes)

IT 53123-88-9, Rapamycin 104987-11-3, FK506
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(role of FKBP12 protein in modulation of **ryanodine receptor calcium** release **channel** function studied by heterologous expression in Sf9 insect cells and Xenopus oocytes)

IT **7440-70-2**, **Calcium**, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(role of FKBP12 protein in modulation of **ryanodine receptor calcium** release **channel** function studied by heterologous expression in Sf9 insect cells and Xenopus oocytes)

L18 ANSWER 20 OF 26 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1995:678075 HCAPLUS
DOCUMENT NUMBER: 123:139283
TITLE: Ultrastructural **immunogold** localization of some organelle-transport relevant proteins in whole-mounted permeabilized non-extracted goldfish xanthophores
AUTHOR(S): Kimler, Victoria A.; Taylor, John D.
CORPORATE SOURCE: Departments Biological Sciences, Wayne State University, Detroit, MI, 48202, USA
SOURCE: Pigment Cell Research (1995), 8(2), 75-82
CODEN: PCREEA; ISSN: 0893-5785
PUBLISHER: Munksgaard
DOCUMENT TYPE: Journal
LANGUAGE: English

AB By whole-cell TEM (WCTEM), the authors recently demonstrated that carotenoid droplets are transported by elongating or retracting endoplasmic reticular cisternae in goldfish xanthophores. Here the authors report that permeabilized xanthophores demonstrate immunogold reactivity against several proteins involved in organelle translocation. The gold labeling against .beta.-tubulin and the intermediate filament protein p45a were found on microtubules and intermediate filaments. Labeling with anti-actin was found on non-identifiable structures, on vesicles of unknown origin, occasional labeling on carotenoid droplets, and on occasional microfilaments. Immunoreactivity was demonstrated with anti-p57 on the carotenoid droplet surface, confirming previous results. Labeling with anti-PCD6 subunit (of the inositol trisphosphate/ryanodine receptor) was demonstrated on carotenoid droplets suggesting they possess calcium channels. Anti-MAP 1C (dynein) immunolabeling was generally seen on club-shaped structures in the cytomatrix and on carotenoid droplets. Finally, immunogold labeling with anti-MAP 2a + 2b was seen on a meshwork

of microfilaments and intermediate filaments. Finally, this is the first report of a WCTEM technique for permeabilized cells that reveals immunoreactive elements, organelles, and cytomatrix components without the addnl. requirements of extn. or fracturing.

CC 12-1 (Nonmammalian Biochemistry)

IT Ion **channel**
(**calcium**, ultrastructural localization of some organelle-transport relevant proteins in whole-mounted permeabilized non-extd. goldfish xanthophores)

IT **Receptors**
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(**ryanodine**, ultrastructural localization of some organelle-transport relevant proteins in whole-mounted permeabilized non-extd. goldfish xanthophores)

L18 ANSWER 21 OF 26 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1993:600168 HCAPLUS
DOCUMENT NUMBER: 119:200168
TITLE: Differential **immunohistochemical** localization of inositol 1,4,5-trisphosphate- and ryanodine-sensitive **calcium** release **channels** in rat brain
AUTHOR(S): Sharp, Alan H.; McPherson, Peter S.; Dawson, Ted M.; Aoki, Chiye; Campbell, Kevin P.; Snyder, Solomon H.
CORPORATE SOURCE: Sch. Med., John Hopkins Univ., Baltimore, MD, 21205, USA
SOURCE: Journal of Neuroscience (1993), 13(7), 3051-63
CODEN: JNRSDS; ISSN: 0270-6474
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Ca2+ release from inositol 1,4,5-trisphosphate (IP3)-sensitive and ryanodine-sensitive intracellular Ca2+ stores is mediated by distinct proteins identified as IP3 receptors (IP3R) and ryanodine receptors (RyR), resp. The authors have compared the immunohistochem. localizations of IP3R and RyR in the brain at the light and electron microscopic levels and have also evaluated the distribution of the major brain intracellular Ca2+-pumping ATPase. IP3R and RyR occur in overlapping populations of neurons in widespread areas of the brain, but labeling is distinct in a no. of areas. For example, IP3R is enriched in cerebellar Purkinje cells and hippocampal CA 1 pyramidal cells, while RyR is present at relatively low levels in these cells. RyR is most enriched in the dentate gyrus and CA3/4 areas of the hippocampus, where IP3R levels are low. In the cortex, IP3R is found in pyramidal cell bodies and proximal dendrites, whereas RyR is located predominantly in long, thin apical dendrites of pyramidal cells. In deep cerebellar nuclei, RyR is located in cell bodies that appear devoid of IP3R, whereas IP3R is enriched in terminals surrounding cell bodies. Electron microscopy in the hippocampus reveals RyR in axons, dendritic spines, and dendritic shafts near dendritic spines while IP3R is primarily identified in dendritic shafts and cell bodies. These results suggest that the IP3- and ryanodine-sensitive Ca2+ pools have largely distinct roles in controlling intracellular Ca2+ levels, though in some sites they may interact to varying degrees.

CC 13-1 (Mammalian Biochemistry)

ST **receptor** inositol trisphosphate **ryanodine** brain; **calcium** inositol trisphosphate **ryanodine** brain

IT Biological transport
(of **calcium**, in rat brain, inositol trisphosphate and ryanodine-sensitive)

IT Receptors

RL: BIOL (Biological study)
(inositol tris(phosphate), of brain, **calcium** release in relation to)
IT **Receptors**
RL: BIOL (Biological study)
(**ryanodine**, of brain, **calcium** release in relation to)
IT 15662-33-6, Ryanodine, 88269-39-0, Inositol 1,4,5-trisphosphate
RL: BIOL (Biological study)
(**calcium** pools of brain region responsive to)
IT 9000-83-3, ATPase
RL: BIOL (Biological study)
(**calcium**-activated, of brain regions)
IT **7440-70-2**, **Calcium**, biological studies
RL: BIOL (Biological study)
(transport of, in brain regions, inositol trisphosphate- and ryanodine-sensitive)

L18 ANSWER 22 OF 26 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1993:576259 HCAPLUS
DOCUMENT NUMBER: 119:176259
TITLE: Characterization of the major brain form of the **ryanodine receptor/calcium** release **channel**
AUTHOR(S): McPherson, Peter S.; Campbell, Kevin P.
CORPORATE SOURCE: Coll. Med., Univ. Iowa, Iowa City, IA, 52242, USA
SOURCE: Journal of Biological Chemistry (1993), 268(26), 19785-90
CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE: Journal
LANGUAGE: English
AB At least three distinct ryanodine receptor genes appear to be expressed in mammalian brain. The authors have used biochem. and immunol. methods to characterize the major form of ryanodine binding protein purified from brain. [3H]Ryanodine binding to the purified brain receptor is stimulated by Ca2+, ATP, KCl, and phosphorylation and is inhibited by calmodulin, Mg2+, and ruthenium red. Immunoblot and immunopptn. anal. using a panel of monoclonal and polyclonal antibodies against skeletal and cardiac muscle ryanodine receptors, and two novel polyclonal antibodies against the brain ryanodine receptor, reveals that the major form of ryanodine receptor expressed in brain is immunol. similar to the cardiac ryanodine receptor, but is distinct from the skeletal muscle receptor. Digestion of cardiac and brain ryanodine receptors with trypsin or .alpha.-chymotrypsin generates similar proteolytic patterns as detected by immunoblot anal. or by autoradiog. after labeling with a hydrophobic probe, suggesting that the two proteins are similar in both their large cytoplasmic and hydrophobic transmembrane domains. Taken together, these data indicate that the cardiac ryanodine receptor/Ca2+ release channel is the major form of ryanodine receptor expressed in brain, and that it likely functions in releasing Ca2+ from caffeine-sensitive intracellular Ca2+ stores in neurons by a mechanism of regulated Ca2+-induced Ca2+ release.
CC 6-3 (General Biochemistry)
ST **ryanodine receptor calcium channel**
brain
IT Phosphorylation, biological
(of **ryanodine receptor/calcium** release **channel** of brain, binding of **ryanodine** stimulation by)
IT Heart, composition
(**ryanodine receptor** of, structural similarities of

brain **ryanodine receptor** and)
IT Calmodulins
RL: BIOL (Biological study)
(**ryanodine receptor/calcium** release
channel of brain binding of **ryanodine** inhibition by)
IT Ionic strength
(**ryanodine receptor/calcium** release
channel of brain binding of **ryanodine** stimulation by)
IT Brain, composition
(**ryanodine receptor/calcium** release
channel of, **ryanodine** binding properties and
structural and **immunol**. characterization of)
IT Ion **channel**
(**calcium**, of **ryanodine receptor** of brain,
structural and **immunol**. characterization of)
IT **Receptors**
RL: BIOL (Biological study)
(**ryanodine**, of brain, **ryanodine** binding properties
and structural and **immunol**. characterization of)
IT 15662-33-6, **Ryanodine**
RL: BIOL (Biological study)
(**receptors** for, of brain, **ryanodine** binding
properties and structural and **immunol**. characterization of)
IT 7439-95-4, Magnesium, biological studies 11103-72-3, Ruthenium red
RL: BIOL (Biological study)
(**ryanodine receptor/calcium** release
channel of brain binding of **ryanodine** inhibition by)
IT 56-65-5, 5'-ATP, biological studies **7440-70-2, Calcium**
, biological studies
RL: BIOL (Biological study)
(**ryanodine receptor/calcium** release
channel of brain binding of **ryanodine** stimulation by)

L18 ANSWER 23 OF 26 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1993:445944 HCAPLUS
DOCUMENT NUMBER: 119:45944
TITLE: Distribution of **ryanodine receptor**
-like **immunoreactivity** in mammalian central
nervous system is consistent with its role in
calcium-induced **calcium** release
AUTHOR(S): Sah, P.; Francis, K.; McLachlan, E. M.; Junankar, P.
CORPORATE SOURCE: Dep. Physiol. Pharmacol., Univ. Queensland, 4072,
Australia
SOURCE: Neuroscience (Oxford, United Kingdom) (1993), 54(1),
157-65
CODEN: NRSCDN; ISSN: 0306-4522
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The distributions of ryanodine receptor-like immunoreactivity and Ca-ATPase-like immunoreactivity were identified in the guinea-pig and rat central nervous system using antibodies raised against the rabbit skeletal muscle ryanodine receptor and Ca-ATPase. In both guinea-pig and rat cerebellum, the ryanodine receptor-like immunoreactivity was restricted to the soma and dendrites of Purkinje cells. In the medulla, neuron somata in the hypoglossal nucleus were stained in both species, but in the dorsal motor nucleus of the vagus somata were stained in guinea-pigs but not in rats. This species difference in ryanodine receptor-like immunoreactivity is consistent with the species difference in expression of a ryanodine-sensitive, calcium-activated potassium conductance in neurons of the dorsal motor nucleus of the vagus. Immunoreactivity to Ca-ATPase was

present in vagal motoneurons in both species with denser staining in the guinea-pig. The data further support the idea that, in neurons of the dorsal motor nucleus of the vagus, release of intracellular calcium stores via a ryanodine receptor activates a specific class of potassium channels, thereby modulating cell excitability.

CC 13-1 (Mammalian Biochemistry)

ST **ryanodine receptor** distribution nervous system

IT Nervous system
(central, **ryanodine receptor** and **calcium** pump distribution in)

IT Brain, composition
(cerebellum, **ryanodine receptor** distribution in)

IT Brain, composition
(medulla oblongata, **ryanodine receptor** distribution in)

IT **Receptors**
RL: BIOL (Biological study)
(**ryanodine**, in central nervous system)

IT Nerve, composition
(vagus, dorsal motor nucleus, **ryanodine receptor** localization in, **calcium**-activated potassium **channels** in relation to)

IT 9000-83-3, ATPase
RL: BIOL (Biological study)
(**calcium**-activated, in central nervous system, **ryanodine receptor** distribution in relation to)

L18 ANSWER 24 OF 26 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1993:98658 HCAPLUS

DOCUMENT NUMBER: 118:98658

TITLE: **Immunohistochemical** localization of **ryanodine receptors** in mouse central nervous system

AUTHOR(S): Nakanishi, Setsuko; Kuwajima, Goro; Mikoshiba, Katsuhiko

CORPORATE SOURCE: Pharm. Basic Res. Lab., Japan Tobacco Inc., Yokohama, 236, Japan

SOURCE: Neuroscience Research (Oxford, United Kingdom) (1992), 15(1-2), 130-42
CODEN: NERADN; ISSN: 0168-0102

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The distribution of ryanodine receptor-like immunoreactivity in the mouse central nervous system was studied using two antibodies raised against synthetic peptides. These peptides represented a region conserved between the cardiac and skeletal muscle forms and a region specific to the cardiac form. Western blotting anal. and [3H]ryanodine binding anal. showed ryanodine receptors are expressed in all the brain regions. The activity was prominent in hippocampus and cerebral cortex. Immunohistochem. study demonstrated that the ryanodine receptors were localized unevenly in somata. Some apical and proximal dendrites in some cells were also labeled. In hippocampus pyramidal neurons in CA2-3 region were labeled more than CA1 region. Immunohistochem. distribution revealed by two antibodies was essentially the same but the fibers were more immunoreactive with the antibody raised against the cardiac muscle ryanodine form. The localization of ryanodine receptors was quite different from that of inositol 1,4,5-trisphosphate receptors.

CC 13-1 (Mammalian Biochemistry)

ST **ryanodine receptor** central nervous system; **calcium** release **channel** phosphoprotein brain

IT Heart, composition
Muscle, composition
(**ryanodine receptor** form specific for, localization of, in brain)
IT Brain, composition
(**ryanodine receptors** of regions of, localization of)
IT Phosphoproteins
RL: PROC (Process)
(**calcium** release **channel**/junctional foot, of central nervous system, localization of)
IT Nerve, composition
(cell body, **ryanodine receptors** of, of brain, localization of)
IT Nervous system
(central, ryanodine-binding **calcium** release **channel** phosphoproteins of, localization of)
IT Brain, composition
(cerebral cortex, **ryanodine receptors** of, localization of)
IT Nerve, composition
(dendrite, **ryanodine receptors** of, of brain, localization of)
IT Brain, composition
(hippocampus, **ryanodine receptors** of, localization of)
IT **Receptors**
RL: PROC (Process)
(inositol tris(phosphate), of central nervous system, localization of, **ryanodine receptors** in relation to)
IT 88269-39-0, Inositol 1,4,5-trisphosphate
RL: BIOL (Biological study)
(**receptors** for, of central nervous system, localization of, **ryanodine receptors** in relation to)

L18 ANSWER 25 OF 26 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1991:59497 HCAPLUS
DOCUMENT NUMBER: 114:59497
TITLE: Biogenesis of transverse tubules and triads: **immunolocalization** of the 1,4-dihydropyridine **receptor**, TS28, and the **ryanodine receptor** in rabbit skeletal muscle developing in situ
AUTHOR(S): Yuan, Shaohua; Arnold, Wayne; Jorgensen, Annelise O.
CORPORATE SOURCE: Dep. Anat., Univ. Toronto, Toronto, ON, Can.
SOURCE: Journal of Cell Biology (1991), 112(2), 289-301
CODEN: JCLBA3; ISSN: 0021-9525
DOCUMENT TYPE: Journal
LANGUAGE: English
AB To extend morphol. studies of the biogenesis of T-tubules and triads, the temporal appearance and subcellular distribution of the .alpha.1-subunit of the 1,4-dihydropyridine receptor (a marker of the T-tubules and caveolae) was compared to (1) that of TS28 (a marker of T-tubules and caveolae); and (2) that of the ryanodine receptor (a marker of the junctional sarcoplasmic reticulum) in rabbit skeletal muscle cells developing in situ (day 19 of gestation to 10 day newborn) by double immunofluorescence labeling. The results presented show that the temporal appearance and relative subcellular distribution of the .alpha.1-subunit of the 1,4-dihydropyridine receptor (.alpha.1-DHPR) are distinct from those of TS28 at the onset of the biogenesis of T-tubules. Thus, in a

particular developing myotube the .alpha.1-DHPR appeared before TS28 (secondary myotubes; day 19-24 of gestation). Furthermore, the .alpha.1-DHPR was distributed in discrete foci at the outer zone of the cytosol, whereas TS28 was confined to foci and rod-like structures at the cell periphery. As development proceeded (primary myotubes; day 24 of gestation) .apprx.50% of the foci were pos. labeled for both TS28 and the .alpha.1-DHPR, whereas .apprx.20 and 30% of the foci were uniquely labeled for TS28 and the .alpha.1-DHPR, resp. The foci labeled for both TS28 and the .alpha.1-DHPR and the foci uniquely labeled for TS28 were generally confined to the cell periphery, whereas the foci uniquely labeled for the .alpha.1-DHPR were mostly confined to the outer zone of the cytosol. 1-2 Day after birth, TS28 was distributed in a chickenwire-like network throughout the cytosol, whereas the .alpha.1-DHPR was confined to cytosolic foci. In contrast, the temporal appearance and subcellular distribution of the .alpha.1-DHPR and the ryanodine receptor were very similar, if not identical, throughout all the stages of the de novo biogenesis of T-tubules and triads examd. Assuming that the subcellular distribution of TS28 represents the distribution of forming T-tubules the results presented are consistent with the following plausible scheme for the biogenesis of T-tubules and triads. Before the onset of T-tubule formation, .alpha.1-DHPR-contg. cytosolic vesicles form a complex with a ryanodine receptor-contg. membrane system (.alpha.1-DHPR: ryanodine receptor-complex). This complex is distributed at the outer zone of the cytosol. After the onset of formation of TS28-contg. T-tubules, the .alpha.1-DHPR ryanodine receptor-complex becomes incorporated into discrete regions of the forming T-tubules at the cell periphery. Assuming that .alpha.1-DHPR is complexed with the ryanodine receptor-contg. membrane system, incorporation of the .alpha.1-DHPR into T-tubules also results in the formation of a junctional complex between T-tubules and the sarcoplasmic reticulum.

CC 13-3 (Mammalian Biochemistry)

ST transverse tubule triad muscle development; dihydropyridine **ryanodine receptor** muscle development; TS28 protein muscle development

IT Development, mammalian
Newborn
(dihydropyridine and **ryanodine receptors** of muscle in, T-tubules and triads formation in relation to)

IT Muscle, composition
(dihydropyridine and **ryanodine receptors** of organelles of, in development)

IT **Receptors**
RL: BIOL (Biological study)
(for **ryanodine**, complexes with dihydropyridine **receptor**, in muscle organelle development)

IT Antibodies
RL: BIOL (Biological study)
(to dihydropyridine and **ryanodine receptors** of muscle T-tubule system and triads)

IT Phosphoproteins
RL: BIOL (Biological study)
(**calcium** release **channel**/junctional foot, complexes, with dihydropyridine receptors, in muscle, in development)

IT Glycoproteins, specific or class
RL: BIOL (Biological study)
(dihydropyridine-binding, complexes, with **ryanodine receptor**, .alpha.1 subunit, in muscle organelles, in development)

IT Embryo
(fetus, dihydropyridine and **ryanodine receptors** of

muscle in, T-tubules and triads formation in relation to)
IT Muscle, composition
(myotubule, dihydropyridine and **ryanodine receptors** of organelles of, in development)
IT Endoplasmic reticulum
(sarcoplasmic reticulum, T-tubules junctional complex between, in muscle development, dihydropyridine and **ryanodine receptors** in relation to)

L18 ANSWER 26 OF 26 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1990:607026 HCAPLUS
DOCUMENT NUMBER: 113:207026
TITLE: Solubilization and biochemical characterization of the high affinity [3H]**ryanodine receptor** from rabbit brain membranes
AUTHOR(S): McPherson, Peter S.; Campbell, Kevin P.
CORPORATE SOURCE: Coll. Med., Univ. Iowa, Iowa City, IA, 52242, USA
SOURCE: Journal of Biological Chemistry (1990), 265(30), 18454-60
CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A high affinity [3H]ryanodine receptor has been solubilized from rabbit brain membranes and biochem. characterized. [3H]ryanodine binding to rabbit brain membranes is specific and saturable, with a Kd of 1.3 nM. [3H]ryanodine binding is enriched in membranes from the hippocampus but is significantly lower in membranes from the brain stem and spinal cord. Approx. 60% of [3H]ryanodine-labeled receptor is solubilized from brain membranes using 2.5% CHAPS and 10 mg/mL phosphatidylcholine contg. 1M NaCl. The solubilized brain [3H]ryanodine receptor sediments through sucrose gradients like the skeletal receptor as a large (.apprx.30 S) complex. Solubilized receptor is specifically immunopptd. by sheep polyclonal antibodies against purified skeletal muscle ryanodine receptor coupled to protein A-Sepharose. [3H]ryanodine-labeled receptor binds to heparin-agarose, and a protein of .apprx.400,000 Da, which is cross-reactive with 2 polyclonal antibodies raised against the skeletal muscle ryanodine receptor, elutes from the column and is enriched in peak [3H]ryanodine binding fractions. These results suggest that the .apprx.400,000-Da protein is the brain form of the high affinity ryanodine receptor and that it shares several properties with the skeletal ryanodine receptor, including a large oligomeric structure composed of .apprx.400,000-Da subunits.
CC 6-3 (General Biochemistry)
Section cross-reference(s): 9, 13
ST **ryanodine receptor** brain membrane; **calcium** release **channel** muscle brain
IT **Receptors**
RL: BIOL (Biological study)
(for **ryanodine**, of brain membrane and other central nervous system regions, muscle sarcoplasmic reticulum **receptor immunocross**-reactivity with and purifn. and properties of)
IT Brain, composition
Spinal cord
(**ryanodine receptor** of membrane of, purifn. and characterization of and skeletal muscles **calcium** release **channel immunocross**-reactivity with)
IT Muscle, composition
(**ryanodine receptor** of membrane of, **receptor** of brain and other central nervous system regions **immunocross**-reactivity with)

IT Membrane, biological
(**ryanodine receptor** of, of brain and other central nervous system regions, purifn. and characterization of and muscle **calcium** release **channel immunocross**-reactivity with)

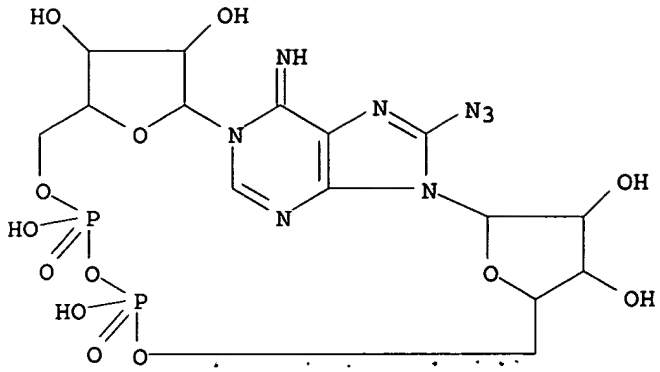
IT Ion **channel**
(**calcium**, ryanodine-binding, of central nervous system membranes, purifn. and properties of)

IT Phosphoproteins
RL: BIOL (Biological study)
(**calcium** release **channel**/junctional foot, ryanodine-binding proteins of brain membrane **immunocross**-reactivity with, of skeletal muscle sarcoplasmic reticulum)

IT Brain, composition
(cerebellum, **ryanodine receptor** of membrane of, purifn. and characterization of and skeletal muscles **calcium** release **channel immunocross**-reactivity with)

IT Brain, composition
(hippocampus, **ryanodine receptor** of membrane of, purifn. and characterization of and skeletal muscles **calcium** release **channel immunocross**-reactivity with)

IT Brain, composition
(stem, **ryanodine receptor** of membrane of, purifn. and characterization of and skeletal muscles **calcium** release **channel immunocross**-reactivity with)



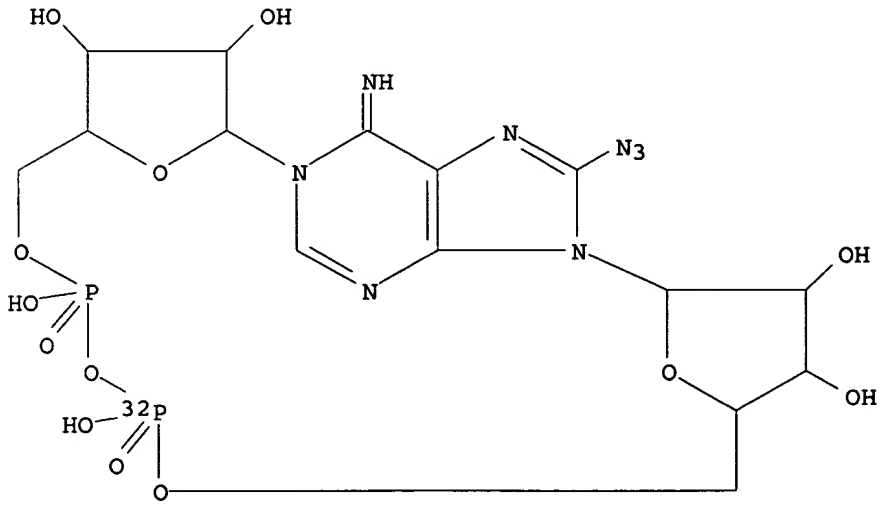
3 REFERENCES IN FILE CA (1962 TO DATE)
3 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 124:317786

REFERENCE 2: 120:28268

REFERENCE 3: 119:244740

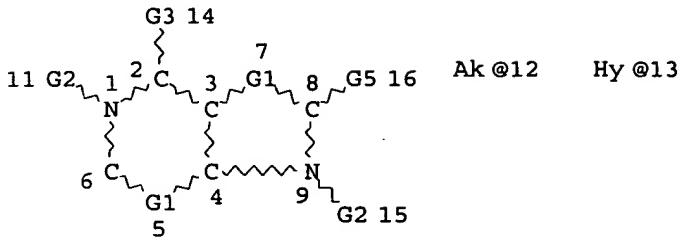
L2 ANSWER 7 OF 7 REGISTRY COPYRIGHT 2002 ACS
RN 150424-93-4 REGISTRY
CN Adenosine 5'-(trihydrogen diphosphate-P-32P), 8-azido-1-.beta.-D-ribofuranosyl-, intramol. P'.fwdarw.5''-ester (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 8-Azido-[32P]cADPR
MF C15 H20 N8 O13 P2
SR CA
LC STN Files: CA, CAPLUS



1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 119:244740

=> d que stat l4
L3 STR



Claim 5

VAR G1=CH/N
VAR G2=H/12/13/P
VAR G3=O/S/N
VAR G5=X/NH
NODE ATTRIBUTES:
CONNECT IS E1 RC AT 12
DEFAULT MLEVEL IS ATOM
GGCAT IS MCY SAT AT 13
DEFAULT ECLEVEL IS LIMITED
ECOUNT IS E4 C E1 O AT 13

GRAPH ATTRIBUTES:
RSPEC I
NUMBER OF NODES IS 15

STEREO ATTRIBUTES: NONE
L4 5452 SEA FILE=REGISTRY SSS FUL L3

100.0% PROCESSED 195844 ITERATIONS 5452 ANSWERS
SEARCH TIME: 00.00.18

=> fil hcaplus
FILE 'HCAPLUS' ENTERED AT 08:58:06 ON 04 NOV 2002
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE COVERS 1907 - 4 Nov 2002 VOL 137 ISS 19
FILE LAST UPDATED: 3 Nov 2002 (20021103/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

CAS roles have been modified effective December 16, 2001. Please check your SDI profiles to see if they need to be revised. For information on CAS roles, enter HELP ROLES at an arrow prompt or use the CAS Roles thesaurus (/RL field) in this file.
'OBI' IS DEFAULT SEARCH FIELD FOR 'HCAPLUS' FILE

=> d his l5-

(FILE 'REGISTRY' ENTERED AT 08:55:25 ON 04 NOV 2002)

FILE 'HCAPLUS' ENTERED AT 08:55:45 ON 04 NOV 2002

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L6        2896 S L4
L7         217 S L6 (L) THU/RL
L8          17 S IMMU? AND L7
L9          16 S L8 NOT L5
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FILE 'REGISTRY' ENTERED AT 08:57:47 ON 04 NOV 2002

FILE 'HCAPLUS' ENTERED AT 08:58:06 ON 04 NOV 2002

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L5 ANSWER 1 OF 13 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2002:122798 HCAPLUS
DOCUMENT NUMBER: 136:177974
TITLE: Nicotinic acid adenine dinucleotide phosphate (NAADP) analogs for modulating T-cell activity
INVENTOR(S): Potter, Barry V. L.; Guse, Andreas H.; Mayr, Georg W.; Berg, Ingeborg
PATENT ASSIGNEE(S): University of Bath, UK
SOURCE: PCT Int. Appl., 83 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002011736	A1	20020214	WO 2001-GB3440	20010731
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2001075732	A5	20020218	AU 2001-75732	20010731

PRIORITY APPLN. INFO.: GB 2000-19234 A 20000804
WO 2001-GB3440 W 20010731

OTHER SOURCE(S): MARPAT 136:177974

AB A method for modulating T cell activity by modulating the intracellular concn. and/or activity of NAADP+, compds. capable of modulating the effect of NAADP+ on T cell Ca+2 levels, and methods for identifying such compds., are described. Prepn. of 8-bromo-nicotinic acid adenine dinucleotide

phosphate is described.

IC ICM A61K031-70
ICS C07H021-02; C07H019-207

CC 1-7 (Pharmacology)
Section cross-reference(s): 33

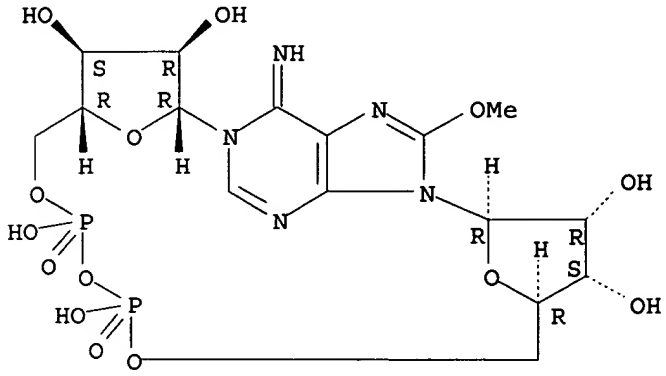
IT 113596-09-1 **398460-86-1**
RL: PAC (Pharmacological activity); BIOL (Biological study)
(NAADP analogs for modulating T-cell activity)

IT **398460-86-1**
RL: PAC (Pharmacological activity); BIOL (Biological study)
(NAADP analogs for modulating T-cell activity)

RN 398460-86-1 HCAPLUS

CN Adenosine 5'-(trihydrogen diphosphate), 8-methoxy-1-.beta.-D-ribofuranosyl-, intramol. P',5''-ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 2 OF 13 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2000:866262 HCAPLUS
DOCUMENT NUMBER: 134:191049
TITLE: Both linopirdine- and WAY123,398-sensitive components of IK(M,ng)are modulated by cyclic ADP ribose in NG108-15 cells
AUTHOR(S): Higashida, Haruhiro; Brown, David A.; Robbins, Jon
CORPORATE SOURCE: Neuroscience Research Centre, Sensory Function Group, King's College, London, SE1 9RT, UK
SOURCE: Pfluegers Archiv (2000), 441(2/3), 228-234
CODEN: PFLABK; ISSN: 0031-6768
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The 'M-like' current in NG108-15 cells has two components carried by different K+ channels: a fast-deactivating component, analogous toIK(M) in sympathetic neurons and carried by KCNQ2/3 channels, and a more slowly deactivating component carried by murine erg1 (merg1) channels. The former is selectively blocked by linopirdine (.ltoreq.10 mM), the latter by WAY123,398 (.ltoreq.10 mM). Bradykinin (100 nM) inhibited 76% of the KCNQ component of current compared with 12% of the merg component. Cyclic ADP ribose (cADPR, 2 mM), introduced via the patch pipet, caused a rundown of both current components. Acetylcholine (100 mM) inhibited 89% of the KCNQ component of current compared to 34% of the merg component. After 15 min of intracellular dialysis with the cADPR antagonist 8-amino-cADP

ribose (100 mM), the inhibition reduced to 40% and 19% and after 30 min it was further reduced to 8% and 5% for the KCNQ currents and merg currents resp. These data show that both KCNQ and merg currents in NG108-15 cells can be modulated by either bradykinin or M1muscarinic receptors. The inhibition of the KCNQ current component is more pronounced than that of the merg component. These results suggest that cADPR might be involved in M1-muscarinic inhibition of both KCNQ2/3 and merg1 channels.

CC 13-2 (Mammalian Biochemistry)

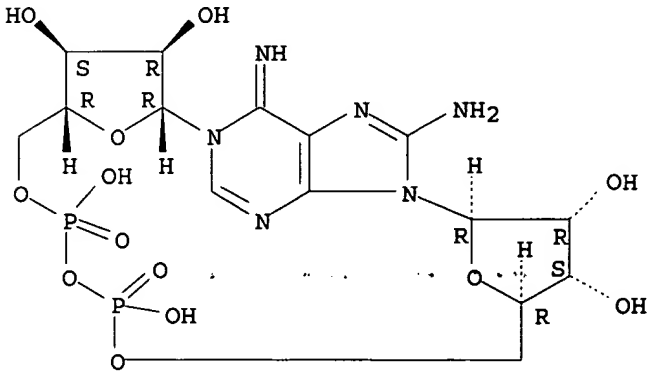
IT 51-84-3, Acetylcholine, biological studies 58-82-2, Bradykinin 119340-53-3, Cyclic ADP ribose **151898-25-8**, 8-Amino-cADPR
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(modulation of linopirdine- and WAY123,398-sensitive components of potassium channels of NG108-15 cells by cyclic ADP ribose, cADP ribose antagonist, bradykinin and acetylcholine)

IT **151898-25-8**, 8-Amino-cADPR
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(modulation of linopirdine- and WAY123,398-sensitive components of potassium channels of NG108-15 cells by cyclic ADP ribose, cADP ribose antagonist, bradykinin and acetylcholine)

RN 151898-25-8 HCAPLUS

CN Adenosine 5'-(trihydrogen diphosphate), 8-amino-1-.beta.-D-ribofuranosyl-, intramol. P'.fwdarw.5''-ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 3 OF 13 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1999:408616 HCAPLUS

DOCUMENT NUMBER: 131:197977

TITLE: An antagonist of cADP-ribose inhibits arrhythmogenic oscillations of intracellular Ca2+ in heart cells

AUTHOR(S): Rakovic, Stevan; Cui, Yi; Iino, Shigeo; Galione, Antony; Ashamu, Gloria A.; Potter, Barry V. L.; Terrar, Derek A.

CORPORATE SOURCE: University Department Of Pharmacology, Oxford University, Oxford, OX1 3QT, UK

SOURCE: Journal of Biological Chemistry (1999), 274(25), 17820-17827
CODEN: JBCHA3; ISSN: 0021-9258

PUBLISHER: American Society for Biochemistry and Molecular Biology

DOCUMENT TYPE: Journal
LANGUAGE: English

AB Oscillations of Ca2+ in heart cells are a major underlying cause of important cardiac arrhythmias, and it is known that Ca2+-induced release of Ca2+ from intracellular stores (the sarcoplasmic reticulum) is fundamental to the generation of such oscillations. There is now evidence that cADP-ribose may be an endogenous regulator of the Ca2+ release channel of the sarcoplasmic reticulum (the ryanodine receptor), raising the possibility that cADP-ribose may influence arrhythmogenic mechanisms in the heart. 8-Amino-cADP-ribose, an antagonist of cADP-ribose, suppressed oscillatory activity assocd. with overloading of intracellular Ca2+ stores in cardiac myocytes exposed to high doses of the .beta.-adrenoreceptor agonist isoproterenol or the Na+/K+-ATPase inhibitor ouabain. The oscillations suppressed by 8-amino-cADP-ribose included intracellular Ca2+ waves, spontaneous action potentials, after-depolarizations, and transient inward currents. Another antagonist of cADP-ribose, 8-bromo-cADP-ribose, was also effective in suppressing isoproterenol-induced oscillatory activity. Furthermore, in the presence of ouabain under conditions in which there was no arrhythmogenesis, exogenous cADP-ribose was capable of triggering spontaneous contractile and elec. activity. Because enzymic machinery for regulating the cytosolic cADP-ribose concn. is present within the cell, the authors propose that 8-amino-cADP-ribose and 8-bromo-cADP-ribose suppress cytosolic Ca2+ oscillations by antagonism of endogenous cADP-ribose, which sensitizes the Ca2+ release channels of the sarcoplasmic reticulum to Ca2+. It therefore seems possible that cADP-ribose may exert influence on arrhythmogenic activity in the heart, particularly under conditions where loading of the sarcoplasmic reticulum with Ca2+ is high, and hence compds. that reduce the actions of endogenous cADP-ribose may prove useful in the treatment of certain cardiac arrhythmias.

CC 14-5 (Mammalian Pathological Biochemistry)
Section cross-reference(s): 1

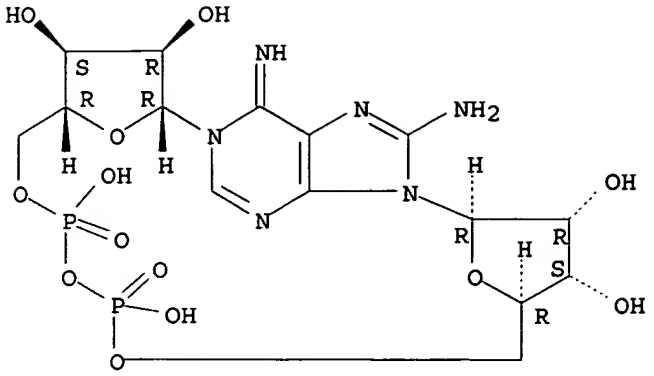
IT 7440-70-2, Calcium, biological studies 119340-53-3, Cyclic ADP-ribose **151898-25-8 151898-26-9**, 8-Bromo-cADP-ribose
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antagonist of cADP-ribose inhibits arrhythmogenic oscillations of intracellular Ca2+ in heart cells in relation to antiarrhythmic activity)

IT **151898-25-8 151898-26-9**, 8-Bromo-cADP-ribose
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antagonist of cADP-ribose inhibits arrhythmogenic oscillations of intracellular Ca2+ in heart cells in relation to antiarrhythmic activity)

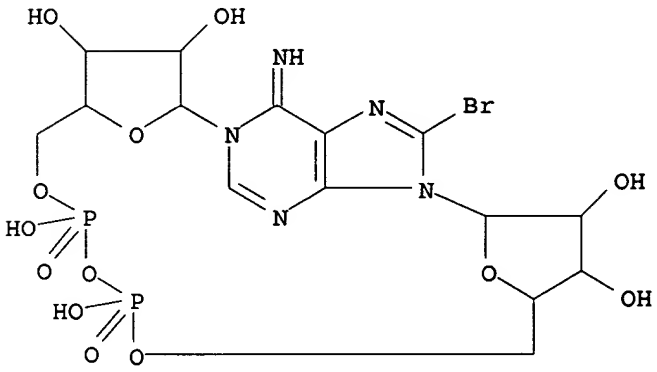
RN 151898-25-8 HCAPLUS

CN Adenosine 5'-(trihydrogen diphosphate), 8-amino-1-.beta.-D-ribofuranosyl-, intramol. P'.fwdarw.5''-ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 151898-26-9 HCAPLUS
CN Adenosine 5'-(trihydrogen diphosphate), 8-bromo-1-.beta.-D-ribofuranosyl-, intramol. P'.fwdarw.5''-ester (9CI) (CA INDEX NAME)



REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 4 OF 13 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:192712 HCAPLUS
DOCUMENT NUMBER: 130:350258
TITLE: Regulation of calcium signalling in T lymphocytes by the second messenger cyclic ADP-ribose
AUTHOR(S): Guse, Andreas H.; Da Silva, Cristina P.; Berg, Ingeborg; Skapenko, Alla L.; Weber, Karin; Heyer, Petra; Hohenegger, Martin; Ashamuf, Gloria A.; Schulze-Koops, Hendrik; Potter, Barry V. L.; Mayr, Georg W.
CORPORATE SOURCE: Department of Enzyme Chemistry, Institute of Physiological Chemistry, University of Hamburg, Hamburg, 20146, Germany
SOURCE: Nature (London) (1999), 398(6722), 70-73
CODEN: NATUAS; ISSN: 0028-0836
PUBLISHER: Macmillan Magazines
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Cyclic ADP-ribose (cADPR) is a natural compd. that mobilizes calcium ions in several eukaryotic cells. Although it can lead to the release of calcium ions in T lymphocytes, it has not been firmly established as a

second messenger in these cells. Here, using high-performance liq. chromatog. anal., we show that stimulation of the T-cell receptor/CD3 (TCR/CD3) complex results in activation of a sol. ADP-ribosyl cyclase and a sustained increase in intracellular levels of cADPR. There is a causal relation between increased cADPR concns., sustained calcium signaling and activation of T cells, as shown by inhibition of TCR/CD3-stimulated calcium signaling, cell proliferation and expression of the early- and late-activation markers CD25 and HLA-DR by using cADPR antagonists. The mol. target for cADPR, the type-3 ryanodine receptor/calcium channel, is expressed in T cells. Increased cADPR significantly and specifically stimulates the apparent assocn. of [3H]ryanodine with the type-3 ryanodine receptor, indicating a direct modulatory effect of cADPR on channel opening. Thus we show the presence, causal relation and biol. significance of the major constituents of the cADPR/calcium-signaling pathway in human T cells.

CC 13-6 (Mammalian Biochemistry)

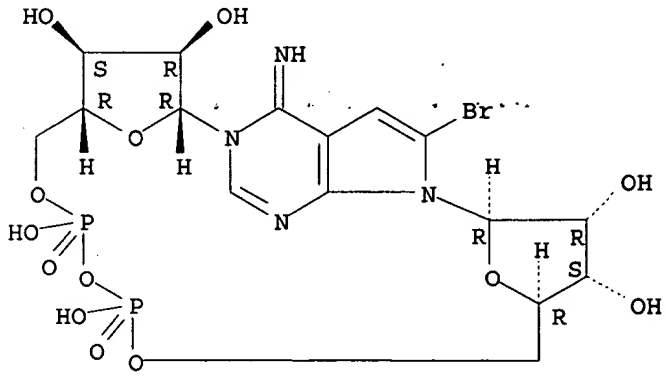
IT 119340-53-3, Cyclic ADP-ribose **189876-06-0**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(regulation of calcium signalling in T lymphocytes by second messenger cyclic ADP-ribose)

IT **189876-06-0**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(regulation of calcium signalling in T lymphocytes by second messenger cyclic ADP-ribose)

RN 189876-06-0 HCAPLUS

CN 4H-Pyrrolo[2,3-d]pyrimidin-4-imine, 6-bromo-3,7-dihydro-3,7-di-.beta.-D-ribofuranosyl-, cyclic P.fwdarw.5':P'.fwdarw.5''-(dihydrogen diphosphate) (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 5 OF 13 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1999:119841 HCAPLUS

DOCUMENT NUMBER: 130:139585

TITLE: Preparation of agonists caged and cyclic nucleotides in study of calcium mobilization in cells and cell homogenates

INVENTOR(S): Gee, Kyle R.; Lee, Hon Cheung; Aarhus, Robert; Haugland, Richard P.; Walseth, Timothy F.; Graeff, Richard M.

PATENT ASSIGNEE(S): Molecular Probes, Inc., USA; The Regents of the University of Minnesota
SOURCE: U.S., 16 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

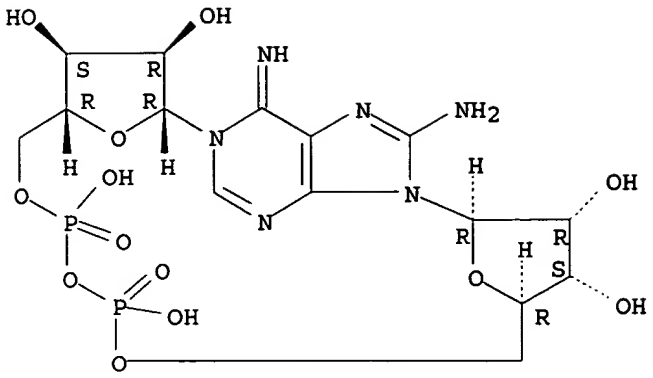
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5872243	A	19990216	US 1995-497183	19950630

OTHER SOURCE(S): MARPAT 130:139585

AB The present invention describes a family of photolabile caged nucleotides, including cyclic nucleotides I (X = independently H, alkali metal, .alpha.-acyloxyalkyl ester; R1 = H, OH, phosphate; R2 = H; R3 = H, single bond with B; B = purine base). The compds. of the present invention are caged analogs and derivs. of NAD+, NADH, NADP, NADPH, NAADP and cADPR. The photolysis of the present compds. allows the release of the free nucleotide in vivo or in vitro with precise spatial and temporal control. The compds. are useful for the photolytic generation of free nucleotides in aq. samples, for example, in the study of calcium mobilization in cells and cell homogenates.

IC ICM C07H001-00
ICS C07H021-00
NCL 536026230
CC 33-9 (Carbohydrates)
Section cross-reference(s): 1
IT 53-57-6DP, NADPH, derivs. 53-59-8DP, NADP, derivs. 58-68-4DP, NADH, derivs. 5502-96-5P, Nicotinic acid adenine dinucleotide phosphate **151898-25-8P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. of agonists caged and cyclic nucleotides in study of calcium mobilization in cells and cell homogenates)
IT **151898-25-8P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. of agonists caged and cyclic nucleotides in study of calcium mobilization in cells and cell homogenates)
RN 151898-25-8 HCAPLUS
CN Adenosine 5'-(trihydrogen diphosphate), 8-amino-1-.beta.-D-ribofuranosyl-, intramol. P'.fwdarw.5''-ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 6 OF 13 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:684854 HCAPLUS
DOCUMENT NUMBER: 129:276237
TITLE: Preparation of cyclic adenosine diphosphate ribose (cADPR) analogs
INVENTOR(S): Galione, Antony; Potter, Barry
PATENT ASSIGNEE(S): ISIS Innovation Ltd., UK; University of Bath
SOURCE: PCT Int. Appl., 30 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9843992	A1	19981008	WO 1998-GB921	19980326
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9868439	A1	19981022	AU 1998-68439	19980326

PRIORITY APPLN. INFO.: GB 1997-6424 19970327
WO 1998-GB921 19980326
OTHER SOURCE(S): MARPAT 129:276237

AB The title analogs (I; .gtoreq.1 of X3, X7 = CR, any remaining X3, X7 = N; Y = halo, C1-20 hydrocarbyl, NR2, OR, SR, NO2, carboxyl; R = H, C1-20 hydrocarbyl; R groups can be the same or different; Z = H; 1 Z can be a caging group), hydrolysis-resistant antagonists of cADPR-induced Ca2+ release, are claimed. Also claimed is compd. II and a method of screening for a compd. which binds to a cADPR receptor. Thus, bromination of tubercidin gave 57% 7-deaza-8-bromoadenosine which was phosphorylated (44%), coupled with NMN (27.7%) and cyclized with ADP-ribosyl cyclase to give II in 31% yield. II has been shown to be a stable, hydrolysis-resistant cADPR antagonist, useful as a tool for investigations of (cADPR)-mediated Ca2+ signalling in intact cells.

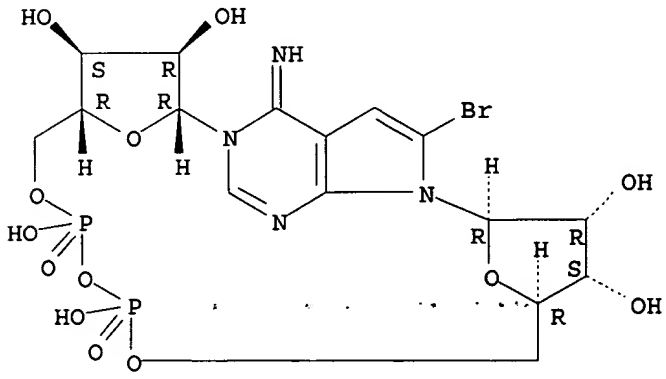
IC ICM C07H019-20

ICS C07H021-00; A61K031-70
CC 33-9 (Carbohydrates)
Section cross-reference(s): 16
IT **213894-69-0P**
RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. of hydrolysis-resistant cyclic ADP ribose analogs as antagonists of cADPR-induced Ca2+ release)
IT **213894-69-0P**
RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. of hydrolysis-resistant cyclic ADP ribose analogs as antagonists of cADPR-induced Ca2+ release)
RN 213894-69-0 HCAPLUS
CN 4H-Pyrrolo[2,3-d]pyrimidin-4-imine, 6-bromo-3,7-dihydro-3-[5-O-[hydroxy(phosphonooxy)phosphinyl]-.beta.-D-ribofuranosyl]-7-.beta.-D-ribofuranosyl-, intramol. P',.fwdarw.5'-ester, compd. with N,N-diethylethanamine (1:1) (9CI) (CA INDEX NAME)

CM 1

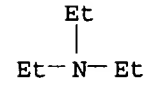
CRN 189876-06-0
CMF C16 H21 Br N4 O13 P2

Absolute stereochemistry.



CM 2

CRN 121-44-8
CMF C6 H15 N



REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 7 OF 13 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:422294 HCAPLUS
DOCUMENT NUMBER: 127:147585
TITLE: 7-Deaza-8-bromo-cyclic ADP-ribose, the first

membrane-permeant, hydrolysis-resistant cyclic ADP-ribose antagonist

AUTHOR(S): Sethi, Jaswinder K.; Empson, Ruth M.; Bailey, Victoria C.; Potter, Barry V. L.; Galione, Antony

CORPORATE SOURCE: University Department Pharmacology, Oxford University, Oxford, OX1 3QT, UK

SOURCE: Journal of Biological Chemistry (1997), 272(26), 16358-16363
CODEN: JBCHA3; ISSN: 0021-9258

PUBLISHER: American Society for Biochemistry and Molecular Biology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Cyclic ADP-ribose (cADPR) is a putative second messenger that has been demonstrated to mobilize Ca2+ in many cell types. Its postulated role as the endogenous regulator of ryanodine-sensitive Ca2+ release channels has been greatly supported by the advent and use of specific cADPR receptor antagonists such as 8-NH2-cADPR (Walseth, T. F., and Lee, H. C. (1993) Biochim. Biophys. Acta 1178, 235-242). However, investigations of the role of cADPR in physiol. responses, such as fertilization, stimulus-secretion coupling, and excitation-contraction coupling, have been hindered by the susceptibility of cADPR receptor antagonists to hydrolysis and the need to introduce these mols. into cells by microinjection or patch clamp techniques. The authors have recently reported on the discovery of a poorly hydrolyzable analog of cADPR, 7-deaza-cADPR (Bailey, V. C., Sethi, J. K., Fortt, S. M., Galione, A., and Potter, B. V. L. (1997) Chem. Biol. 4, 41-51) but this, like cADPR, is an agonist of ryanodine-sensitive Ca2+ release channels. The authors therefore explored the possibility of combining antagonistic activity with that of hydrolytic resistance and now report on the biol. properties of the first hydrolysis-resistant cADPR receptor antagonist, 7-deaza-8-bromo-cADPR. In addn. this compd. has the advantage of being membrane-permeable. Together these properties make this hybrid mol. the most powerful tool to date for studying cADPR-mediated Ca2+ signaling in intact cells.

CC 13-7 (Mammalian Biochemistry)

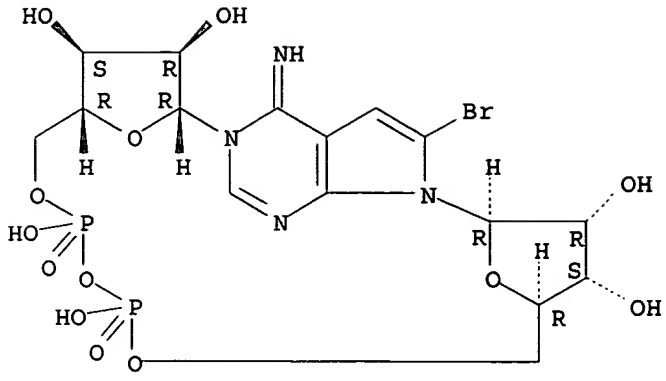
IT **189876-06-0**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); PROC (Process); USES (Uses)
(7-Deazabromo-cyclic ADP-ribose as first membrane-permeant hydrolysis-resistant cyclic ADP-ribose antagonist)

IT **189876-06-0**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); PROC (Process); USES (Uses)
(7-Deazabromo-cyclic ADP-ribose as first membrane-permeant hydrolysis-resistant cyclic ADP-ribose antagonist)

RN 189876-06-0 HCAPLUS

CN 4H-Pyrrolo[2,3-d]pyrimidin-4-imine, 6-bromo-3,7-dihydro-3,7-di-.beta.-D-ribofuranosyl-, cyclic P.fwdarw.5':P'.fwdarw.5''-(dihydrogen diphosphate) (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L5 ANSWER 8 OF 13 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:275719 HCAPLUS
DOCUMENT NUMBER: 126:343786
TITLE: Synthesis of 7-deaza-8-bromo cyclic adenosine 5'-diphosphate ribose: the first hydrolysis resistant antagonist at the cADPR receptor
AUTHOR(S): Bailey, Victoria C.; Sethi, Jaswinder K.; Galione, Antony; Potter, Barry V. L.
CORPORATE SOURCE: Department of Medicinal Chemistry, School of Pharmacy and Pharmacology, University of Bath, Bath, BA2 7AY, UK
SOURCE: Chemical Communications (Cambridge) (1997), (7), 695-696
CODEN: CHCOFS; ISSN: 1359-7345
PUBLISHER: Royal Society of Chemistry
DOCUMENT TYPE: Journal
LANGUAGE: English

AB 7-Deaza-8-bromo cyclic ADP ribose is synthesized from 7-deazaadenosine via 7-deaza-8-bromo NAD; it is both more potent antagonist than the 8-bromo deriv. and has the advantage of chem. and enzymic hydrolytic stability.

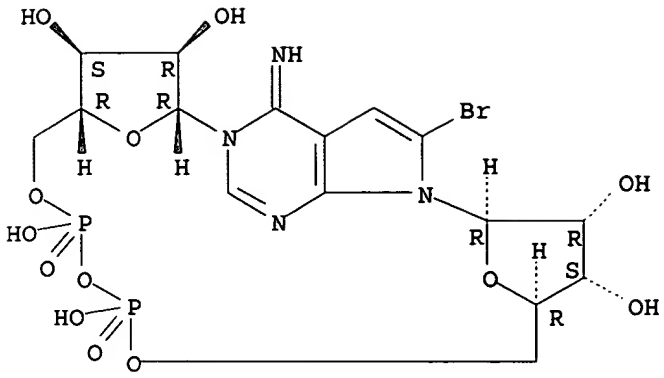
CC 33-9 (Carbohydrates)
Section cross-reference(s): 1

IT **189876-06-0P**
RL: BAC (Biological activity or effector, except adverse); BPN (Biosynthetic preparation); BSU (Biological study, unclassified); BIOL (Biological study); PREP (Preparation)
(prepn. of deazabromo cyclic ADP ribose as the first hydrolysis resistant antagonist at the cADPR receptor)

IT **189876-06-0P**
RL: BAC (Biological activity or effector, except adverse); BPN (Biosynthetic preparation); BSU (Biological study, unclassified); BIOL (Biological study); PREP (Preparation)
(prepn. of deazabromo cyclic ADP ribose as the first hydrolysis resistant antagonist at the cADPR receptor)

RN 189876-06-0 HCAPLUS
CN 4H-Pyrrolo[2,3-d]pyrimidin-4-imine, 6-bromo-3,7-dihydro-3,7-di-.beta.-D-ribofuranosyl-, cyclic P.fwdarw.5':P'.fwdarw.5''-(dihydrogen diphosphate) (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L5 ANSWER 9 OF 13 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1996:499756 HCAPLUS
DOCUMENT NUMBER: 125:191842
TITLE: A specific cyclic ADP-ribose antagonist inhibits cardiac excitation-contraction coupling
AUTHOR(S): Rakovic, Stevan; Galione, Antony; Ashamu, Gloria A.; Potter, Barry V. L.; Terrar, Derek A.
CORPORATE SOURCE: Univ. Dep. Pharmacol., Oxford, OX1 3QT, UK
SOURCE: Current Biology (1996), 6(8), 989-996
CODEN: CUBLE2; ISSN: 0960-9822
PUBLISHER: Current Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Background: Cyclic ADP-ribose (cADPR) has been shown to act as a potent cytosolic mediator in a variety of tissues, regulating the release of Ca2+ from intracellular stores by a mechanism that involves ryanodine receptors. There is controversy over the effects of cADPR in cardiac muscle, although one possibility is that endogenous cADPR increases the Ca2+-induced Ca2+ release (CICR) from the sarcoplasmic reticulum. We investigated this possibility using 8-amino-cADPR, which has been found to antagonize the Ca2+-releasing effects of cADPR on sea urchin egg microsomes and in mammalian cells (Purkinje neurons, Jurkat T cells, smooth muscle and PC12 cells). Results: In intact cardiac myocytes isolated from guinea-pig ventricle, cytosolic injection of 8-amino-cADPR substantially reduced contractions and Ca2+ transients accompanying action potentials (stimulated at 1 Hz). These redns. were not seen with injection of HEPES buffer, with heat-inactivated 8-amino-cADPR, or in cells pretreated with ryanodine (2 .mu.M) to suppress sarcoplasmic reticulum function before injection of the 8-amino-cADPR. L-type Ca2+ currents and the extent of Ca2+ loading of the sarcoplasmic reticulum were not reduced by 8-amino-cADPR. Conclusions: These observations are consistent with the hypothesis that endogenous cADPR plays an important role during normal contractions of cardiac myocytes. One possibility is that cADPR sensitizes the CICR mechanism to Ca2+, an action antagonized by 8-amino-cADPR (leading to reduced Ca2+ transients and contractions). A direct effect of 8-amino-cADPR on CICR cannot be excluded, but observations with caffeine are not consistent with a nonselective block of release channels.

CC 13-6 (Mammalian Biochemistry)
Section cross-reference(s): 6

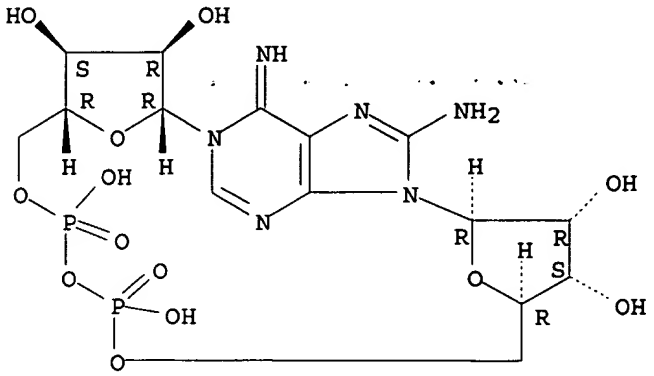
IT **151898-25-8**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

(in intact cardiac myocytes isolated from guinea-pig ventricle, cytosolic injection of 8-amino-cADP ribose substantially reduced contractions and Ca2+ transients accompanying action potentials)

IT **151898-25-8**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(in intact cardiac myocytes isolated from guinea-pig ventricle, cytosolic injection of 8-amino-cADP ribose substantially reduced contractions and Ca2+ transients accompanying action potentials)

RN 151898-25-8 HCAPLUS
CN Adenosine 5'-(trihydrogen diphosphate), 8-amino-1-.beta.-D-ribofuranosyl-, intramol. P'.fwdarw.5''-ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L5 ANSWER 10 OF 13 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1996:123905 HCAPLUS
DOCUMENT NUMBER: 124:317786
TITLE: Cyclic ADP ribose antagonists capable of both inhibiting the release and inhibiting the potentiation of the release of calcium(2+) by cADPR
INVENTOR(S): Walseth, Timothy F.; Lee, Hon Cheung; Aarhus, Robert A.
PATENT ASSIGNEE(S): University of Minnesota, USA
SOURCE: U.S., 18 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5486604	A	19960123	US 1993-148646	19931101

OTHER SOURCE(S): MARPAT 124:317786

AB Cyclic ADP-ribose (cADPR) 8-X analogs I (X = amino, azido, Br) were synthesized and shown to block cADPR from releasing Ca+2, and also inhibit cADPR from potentiating Ca+2 release induced by either divalent cations (Ca+2, Sr+2) or by caffeine. 8-Br- and 8-azido-cADPR were antagonists with less potency than 8-amino-cADPR. These results show that alterations at the 8-position of the adenine group do not inhibit cADPR from binding to its receptor but do eliminate the ability of the metabolite to activate the Ca+2 release mechanism. Thus, e.g., 8-amino-AMP was prepd. by treatment of 8-azido-AMP with dithiothreitol and coupled to .beta.-NMN by

carbodiimide coupling; the resultant 8-amino-NAD+ was converted to 8-amino cADPR (II) using ADP-ribosyl cyclase. Addn. of II to a final concn. of 150 nM to sea urchin egg homogenates did not cause any Ca+2 release by itself but inhibited cADPR (135 nM) added subsequently from releasing Ca+2. Concn.-response curves showed that II was a reversible antagonist of cADPR. Radiolabeling studies showed that II was an effective competitor for the cADPR binding site.

IC ICM C07H019-23
ICS A61K051-00

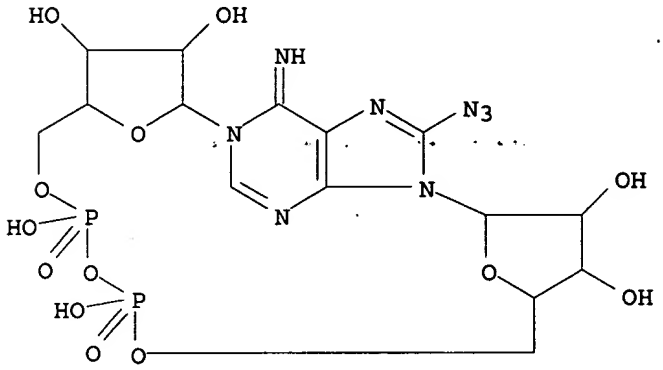
NCL 536026130

CC 33-9 (Carbohydrates)
Section cross-reference(s): 1, 6, 63

IT **150424-94-5P**, 8-Azido-cADPR **151898-25-8P**, 8-Amino-cADPR **151898-26-9P**, 8-Bromo-cADPR
RL: BAC (Biological activity or effector, except adverse); BPN (Biosynthetic preparation); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(cyclic ADP ribose antagonists capable of both inhibiting the release and inhibiting the potentiation of the release of calcium(2+) by cADPR)

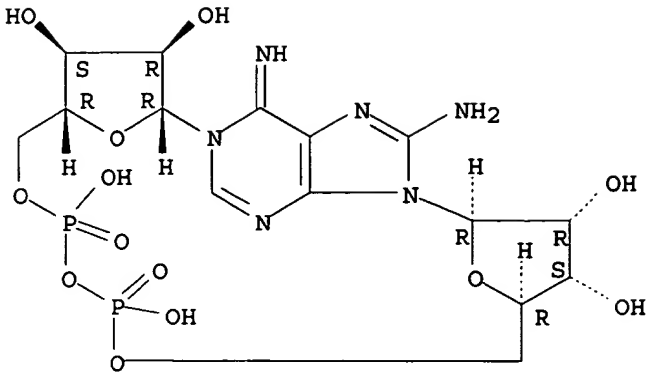
IT **150424-94-5P**, 8-Azido-cADPR **151898-25-8P**, 8-Amino-cADPR **151898-26-9P**, 8-Bromo-cADPR
RL: BAC (Biological activity or effector, except adverse); BPN (Biosynthetic preparation); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(cyclic ADP ribose antagonists capable of both inhibiting the release and inhibiting the potentiation of the release of calcium(2+) by cADPR)

RN 150424-94-5 HCAPLUS
CN Adenosine 5'-(trihydrogen diphosphate), 8-azido-1-.beta.-D-ribofuranosyl-, intramol. P'.fwdarw.5''-ester (9CI) (CA INDEX NAME)

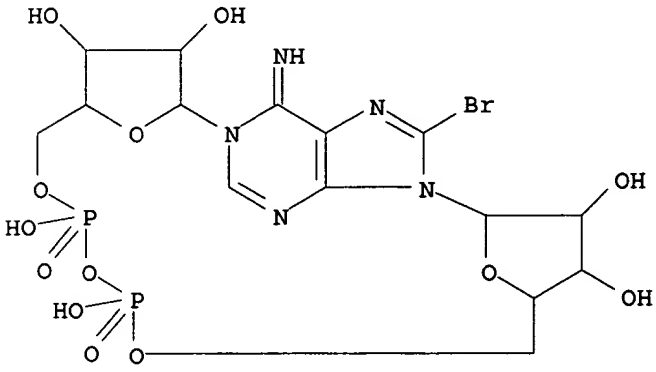


RN 151898-25-8 HCAPLUS
CN Adenosine 5'-(trihydrogen diphosphate), 8-amino-1-.beta.-D-ribofuranosyl-, intramol. P'.fwdarw.5''-ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 151898-26-9 HCAPLUS
CN Adenosine 5'-(trihydrogen diphosphate), 8-bromo-1-.beta.-D-ribofuranosyl-, intramol. P'.fwdarw.5''-ester (9CI) (CA INDEX NAME)



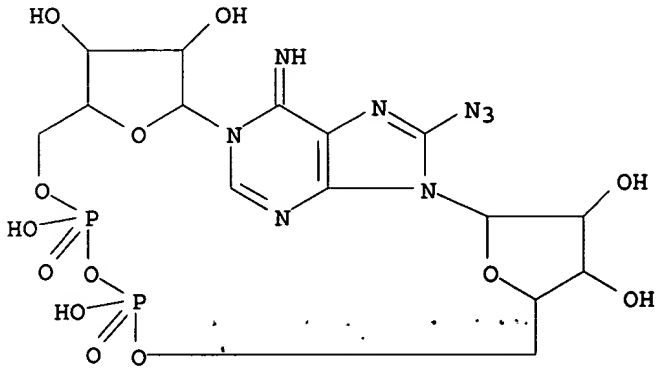
L5 ANSWER 11 OF 13 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1995:672940 HCAPLUS
DOCUMENT NUMBER: 123:340712
TITLE: Chemoenzymic synthesis of analogs of the second messenger candidate cyclic adenosine 5'-diphosphate ribose
AUTHOR(S): Ashamu, Gloria A.; Galione, Antony; Potter, Barry V. L.
CORPORATE SOURCE: Dep. Med. Chem., Univ. Bath, Claverton Down, Bath, BA2 7AY, UK
SOURCE: Journal of the Chemical Society, Chemical Communications (1995), (13), 1359-60
CODEN: JCCCAT; ISSN: 0022-4936
PUBLISHER: Royal Society of Chemistry
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A broad substrate specificity for ADP ribosyl cyclase is demonstrated by cyclization of ribose- and purine-modified NAD analogs to mimics of cyclic ADP ribose, generating a straightforward route for structural modification of this important Ca2+-mobilizing nucleotide. In Ca2+-release studies using sea urchin microsomes, the analogs 2'-deoxy-cADPR, 3'-deoxy-cADPR were active, 8-amino-cADPR was an antagonist, and 8-piperidino-cADPR was inactive.

CC 33-9 (Carbohydrates)
Section cross-reference(s): 2, 7
IT 119340-53-3DP, Cyclic ADP ribose, analogs 170869-44-0P
170869-45-1P 170869-46-2P 170869-47-3P
RL: BAC (Biological activity or effector, except adverse); BPN (Biosynthetic preparation); BSU (Biological study, unclassified); BIOL (Biological study); PREP (Preparation)
(chemoenzymic prepn. and calcium-releasing activity of cyclic ADP ribose analogs)
IT **170869-45-1P**
RL: BAC (Biological activity or effector, except adverse); BPN (Biosynthetic preparation); BSU (Biological study, unclassified); BIOL (Biological study); PREP (Preparation)
(chemoenzymic prepn. and calcium-releasing activity of cyclic ADP ribose analogs)
RN 170869-45-1 HCAPLUS

L5 ANSWER 12 OF 13 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1994:28268 HCAPLUS
DOCUMENT NUMBER: 120:28268
TITLE: Synthesis and characterization of antagonists of cyclic-ADP-ribose-induced Ca2+ release
AUTHOR(S): Walseth, Timothy F.; Lee, Hon Cheung
CORPORATE SOURCE: Department of Pharmacology, University of Minnesota, Minneapolis, MN, USA
SOURCE: Biochimica et Biophysica Acta (1993), 1178(3), 235-42
CODEN: BBACAQ; ISSN: 0006-3002
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Cyclic ADP-ribose (cADPR) is a naturally-occurring metabolite of NAD+ that is as effective as inositol trisphosphate in mobilizing intracellular Ca2+. Analogs modified at the 8-position of the adenine group were synthesized for the study of the relation between the structure of the metabolite and its Ca2+-mobilizing activity. Substitution with an amino group at the 8-position of the adenine ring produced an antagonist. The 1H-NMR spectrum of 8-amino-cADPR showed characteristics of that of cADPR and confirmed the replacement of the 8-proton. By itself, 8-amino-cADPR (150 nM) did not induce Ca2+ release from sea-urchin-egg homogenates but totally blocked cADPR (135 nM) from doing so. The effect was reversible, since high concns. of cADPR could overcome the inhibition. Addn. of 8-amino-cADPR to egg homogenates during the cADPR-induced Ca2+ release blocked the release immediately, demonstrating the effectiveness of the antagonist. Measurements of [32P]cADPR binding to its microsomal binding site showed that 8-amino-cADPR was as effective as cADPR itself in competing for the binding site. In addn. to blocking cADPR from releasing Ca2+, 8-amino-cADPR also inhibited cADPR from potentiating Ca2+-release induced by either divalent cations or by caffeine. Two other 8-substituted analogs were also synthesized. Both 8-Br- and 8-azido-cADPR were also antagonists, although with less potency than 8-amino-cADPR. Alterations at the 8-position of the adenine group do not inhibit cADPR from binding to its receptor but do eliminate the ability of the metabolite to activate the Ca2+-release mechanism.
CC 13-7 (Mammalian Biochemistry)
Section cross-reference(s): 33
IT **150424-94-5P 151898-25-8P 151898-26-9P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of and calcium mobilization response to, structure in relation to)
IT **150424-94-5P 151898-25-8P 151898-26-9P**
RL: SPN (Synthetic preparation); PREP (Preparation)

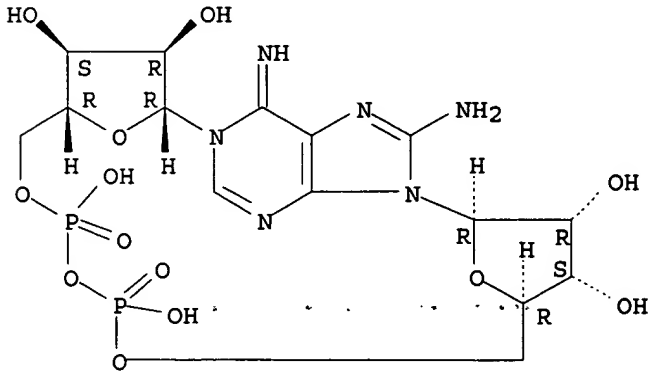
(prepn. of and calcium mobilization response to, structure in relation to)

RN 150424-94-5 HCAPLUS
CN Adenosine 5'-(trihydrogen diphosphate), 8-azido-1-.beta.-D-ribofuranosyl-, intramol. P'.fwdarw.5''-ester (9CI) (CA INDEX NAME)

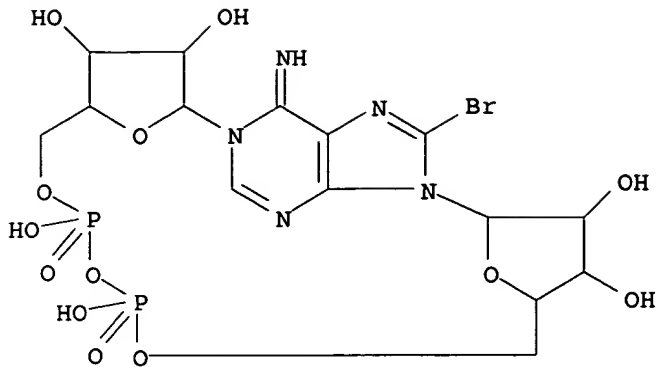


RN 151898-25-8 HCAPLUS
CN Adenosine 5'-(trihydrogen diphosphate), 8-amino-1-.beta.-D-ribofuranosyl-, intramol. P'.fwdarw.5''-ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 151898-26-9 HCAPLUS
CN Adenosine 5'-(trihydrogen diphosphate), 8-bromo-1-.beta.-D-ribofuranosyl-, intramol. P'.fwdarw.5''-ester (9CI) (CA INDEX NAME)



L5 ANSWER 13 OF 13 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1993:644740 HCAPLUS
DOCUMENT NUMBER: 119:244740
TITLE: Identification of cyclic ADP-ribose-binding proteins by photoaffinity labeling
AUTHOR(S): Walseth, Timothy F.; Aarhus, Robert; Kerr, James A.; Lee, Hon Cheung
CORPORATE SOURCE: Dep. Pharmacol., Univ. Minnesota, Minneapolis, MN, 55455, USA
SOURCE: Journal of Biological Chemistry (1993), 268(35), 26686-91
CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The authors synthesized 8-azido-cyclic ADP-ribose (8N3-cADPR) and [32P]8-azido-cyclic ADP-ribose ([32P]8N3-cADPR) to characterize cyclic ADP-ribose (cADPR)-binding sites in sea urchin egg homogenates. 8N3-cADPR was an antagonist of cADPR since it did not induce Ca2+ release from egg microsomes but did inhibit the ability of cADPR to do so. The effect of 8N3-cADPR was reversible and could be overcome by high concns. of cADPR, suggesting that both were acting on the same site. This was supported by the fact that 8N3-cADPR effectively competed for [32P]cADPR binding to microsomes. Reciprocally, binding of [32P]8N3-cADPR could also be selectively displaced by cADPR and 8N3-cADPR, but not by ADP-ribose. These results indicate that SN3-cADPR binds specifically to the cADPR-binding sites and inhibits cADPR from releasing Ca2+. Photolysis of microsomes preincubated with [32P]8N3-cADPR resulted in specific binding of proteins of 140 and 100 kDa, which could be prevented by 8N3-cADPR or nanomolar concns. of cADPR, but not by micromolar concns. of ADP-ribose, AMP, ADP, ATP, cAMP or inositol 1,4,5-trisphosphate. Caffeine, an agonist of Ca2+-induced Ca2+ release, preferentially inhibited the labeling of the 100 kDa as compared to the 140-kDa protein. These results suggest that cADPR may not interact directly with the ryanodine receptor, but may instead, exert its effect through intermediate proteins.

CC 9-5 (Biochemical Methods)
Section cross-reference(s): 12

IT **150424-94-5**
RL: ANST (Analytical study)
(photoaffinity labeling by, of cyclic ADP ribose-binding proteins of sea urchin egg)

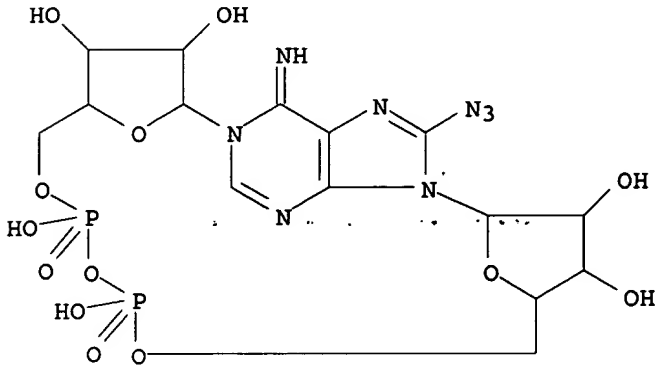
IT **150424-93-4P**
RL: PREP (Preparation)
(prepn. and photoaffinity labeling by, of cyclic ADP-ribose-binding

proteins of sea urchin egg)

IT **150424-94-5**
RL: ANST (Analytical study)
(photoaffinity labeling by, of cyclic ADP ribose-binding proteins of sea urchin egg)

RN 150424-94-5 HCAPLUS

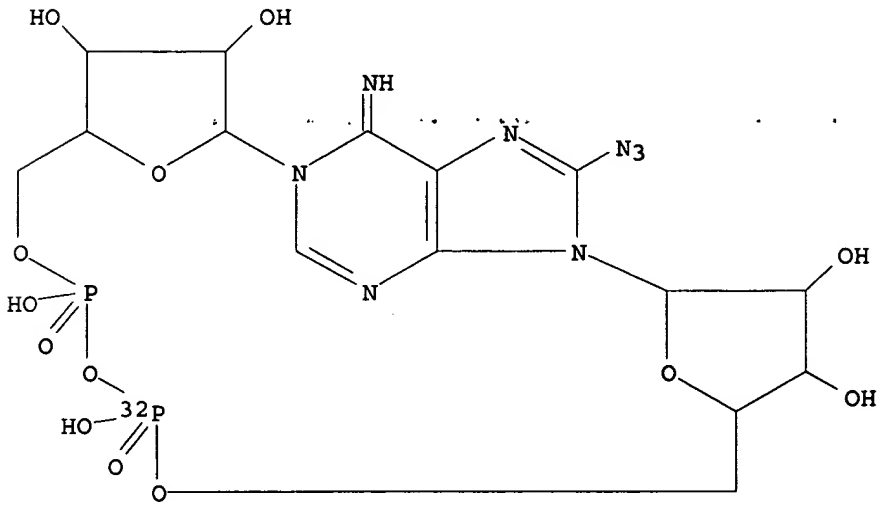
CN Adenosine 5'-(trihydrogen diphosphate), 8-azido-1-.beta.-D-ribofuranosyl-, intramol. P'.fwdarw.5''-ester (9CI) (CA INDEX NAME)



IT **150424-93-4P**
RL: PREP (Preparation)
(prepn. and photoaffinity labeling by, of cyclic ADP-ribose-binding proteins of sea urchin egg)

RN 150424-93-4 HCAPLUS

CN Adenosine 5'-(trihydrogen diphosphate-P-32P), 8-azido-1-.beta.-D-ribofuranosyl-, intramol. P'.fwdarw.5''-ester (9CI) (CA INDEX NAME)



L9 ANSWER 1 OF 16 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:792223 HCAPLUS

DOCUMENT NUMBER: 135:348878
TITLE: Therapeutic treatment and prevention of infections with a bioactive materials encapsulated within a biodegradable-biocompatible polymeric matrix
INVENTOR(S): Setterstrom, Jean A.; Van Hamont, John E.; Reid, Robert H.; Jacob, Elliot; Jeyanthi, Ramasubbu; Boedeker, Edgar C.; Mcqueen, Charles E.; Jarboe, Daniel L.; Cassels, Frederick; Brown, William; Thies, Curt; Tice, Thomas R.; Roberts, F. Donald; Friden, Phil
PATENT ASSIGNEE(S): United States of America as Represented by the Secretary of the Army, USA
SOURCE: U.S., 141 pp., Cont.-in-part of U.S. Ser. No. 590,973, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 12
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6309669	B1	20011030	US 1997-789734	19970127
US 5417986	A	19950523	US 1992-867301	19920410
US 6410056	B1	20020625	US 1995-446148	19950522
US 6447796	B1	20020910	US 1997-920326	19970821
WO 9832427	A1	19980730	WO 1998-US1556	19980127
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9863175	A1	19980818	AU 1998-63175	19980127

PRIORITY APPLN. INFO.:

US 1984-590308	B1	19840316
US 1992-867301	A2	19920410
US 1995-446148	A2	19950522
US 1995-446149	B2	19950522
US 1996-590973	B2	19960124
US 1990-493597	B2	19900315
US 1990-521945	B2	19900511
US 1991-690485	B2	19910424
US 1991-805721	B2	19911121
US 1994-209350	B2	19940107
US 1994-242960	A2	19940516
US 1996-675895	A2	19960705
US 1996-698896	A2	19960816
US 1997-789734	A2	19970127
WO 1998-US1556	W	19980127

AB Novel burst-free, sustained-release biocompatible and biodegradable microcapsules which can be programmed to release their active core for variable durations ranging from 1-100 days in an aq. physiol. environment are disclosed. The microcapsules are comprised of a core of polypeptide or other biol. active agent encapsulated in a matrix of poly(lactide/glycolide) copolymer, which may contain a pharmaceutically-acceptable adjuvant, as a blend of upcapped free carboxyl end group and end-capped forms ranging in ratios from 100/0 to 1/99. Ampicillin microcapsules effectively prevented infection in 73% of rats

whose wound were inoculated with ampicillin-resistant strains of Staphilococcus aureus, while systemic ampicillin failed in 100% of animals.

IC A61K009-52; A61K047-30
NCL 424486000
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1
IT **Immunostimulants**
(adjuvants; therapeutic treatment and prevention of infections with bioactive materials encapsulated within biodegradable-biocompatible polymeric matrix)
IT Absidia ramosa
Actinobacillus equuli
Actinobacillus seminis
Adrenoceptor agonists
Allergy inhibitors
Analgesics
Anesthetics
Anti-inflammatory agents
Antiarrhythmics
Antibacterial agents
Antibiotics
Anticoagulants
Anticonvulsants
Antidepressants
Antiemetics
Antihistamines
Antihypertensives
Antimalarials
Antimigraine agents
Antiparkinsonian agents
Antipyretics
Antitumor agents
Antitussives
Antiviral agents
Appetite depressants
Arcanobacterium pyogenes
Aspergillus fumigatus
Babesia caballi
Bile
Blood plasma
Bovine herpesvirus 1
Bronchodilators
Brucella melitensis
Campylobacter fetus
Campylobacter fetus intestinalis
Candida albicans
Candida tropicalis
Cardiotonics
Cardiovascular agents
Cardiovascular system
Chlamydia psittaci
Cholinergic agonists
Clostridium tetani
Contraceptives
Cytotoxic agents
Decongestants
Digesters
Diuretics
Electrolytes

Encapsulation
Equid herpesvirus 1
Equine arteritis virus
Escherichia coli
Expectorants
Fungicides
Gardnerella vaginalis
Haemophilus ducreyi
Human herpesvirus 1
Human herpesvirus 2
Hypnotics and Sedatives
Immunomodulators
Leptospira interrogans pomona
Listeria monocytogenes
Microorganism
Muscle relaxants
Mycobacterium tuberculosis
Mycoplasma bovigenitalium
Mycoplasma hominis
Narcotics
Neisseria gonorrhoeae
Nutrients
Opioid antagonists
Parasiticides
Pseudomonas aeruginosa
Psychotropics
Rhodococcus equi
Salmonella abortus
Salmonella abortusovis
Stabilizing agents
Streptocarpus
Surfactants
Toxoplasma gondii
Tranquilizers
Treponema pallidum
Trichomonas vaginalis
Tritrichomonas foetus
Trypanosoma equiperdum
Vaccines
Vasodilators
Wound healing
(therapeutic treatment and prevention of infections with bioactive materials encapsulated within biodegradable-biocompatible polymeric matrix)

IT 50-06-6, Phenobarbital, biological studies 50-12-4, Mephenytoin 50-18-0, Cyclophosphamide 50-23-7, Hydrocortisone 50-24-8, Prednisolone 50-28-2, .beta.-Estradiol, biological studies 50-33-9, Phenylbutazone, biological studies 50-52-2, Thioridazine 50-55-5, Reserpine 50-78-2, Aspirin 51-55-8, Atropine, biological studies 52-24-4, Thiotepa 52-76-6, Lynestrenol 53-03-2, Prednisone 53-16-7, Estrone, biological studies 53-86-1, Indomethacin 54-11-5, Nicotine; 55-48-1, Atropine sulfate 55-63-0, Nitroglycerin 55-86-7, Nitrogen mustard 56-53-1, Diethyl stilbestrol 56-75-7, Chloramphenicol 57-27-2, Morphine, biological studies 57-33-0, Sodium pentobarbital 57-42-1, Meperidine 57-53-4, Meprobamate 57-63-6, Ethinyl estradiol 57-85-2, Testosterone propionate 57-92-1, Streptomycin A, biological studies 58-08-2, Caffeine, biological studies 58-14-0, Pyrimethamine 58-22-0, Testosterone 58-25-3, Chlordiazepoxide 58-39-9, Perphenazine 58-73-1, Diphenhydramine 59-01-8, Kanamycin A 59-05-2, Methotrexate 59-92-7, L-Dopa, biological studies 61-33-6, Penicillin G, biological

studies 67-20-9, Nitro-furantoin 68-22-4, Norethindrone 68-23-5, Norethynodrel 69-53-4, Ampicillin 69-72-7D, Salicylic acid, derivs. 71-58-9, Medroxyprogesterone acetate 72-33-3, Mestranol 76-57-3, Codeine 78-11-5, Pentaerythritol tetranitrate 79-57-2, Oxytetracycline 79-64-1, Dimethisterone 91-81-6, Tripelennamine 103-90-2, Acetaminophen 113-15-5, Ergotamine 114-07-8, Erythromycin 114-49-8, Hyoscine hydrobromide 121-54-0, Benzethonium chloride 122-09-8, Phentermine 125-29-1, Dihydrocodeinone 125-71-3, Dextromethorphan 127-48-0, Trimethadione 128-62-1, Noscapine 145-94-8, Chlorindanol 155-41-9, Methscopolamine bromide 288-32-4D, Imidazole, derivs. 297-76-7, Ethynodiol diacetate 302-22-7, Chlormadinone acetate 305-03-3, Chlorambucil 309-43-3, Sodium secobarbital 315-30-0, Allopurinol 434-03-7, Ethisterone 439-14-5, Diazepam 443-48-1, Metronidazole 469-62-5 471-34-1, Calcium carbonate, biological studies 497-19-8, Sodium carbonate, biological studies **523-87-5**, Dimenhydrinate 546-93-0, Magnesium carbonate 578-66-5D, 8 Aminoquinoline, derivs. 578-68-7D, 4-Aminoquinoline, derivs. 595-33-5, Megestrol acetate 738-70-5, Trimethoprim 846-50-4, Temazepam 1397-89-3, Amphotericin-B 1397-94-0, Antimycin A 1403-66-3, Gentamicin 1404-26-8, Polymyxin-B; 1404-90-6, Vancomycin 1406-05-9, Penicillin 4696-76-8, Kanamycin B 5588-33-0, Mesoridazine 5633-18-1, Melengestrol 5786-21-0, Clozapine 5800-19-1, Metiapine 6533-00-2, Norgestrel 7447-40-7, Potassium chloride, biological studies 8063-07-8, Kanamycin 9000-83-3, Adenosine triphosphatase 9000-92-4, Amylase 9001-46-1, Glutamic acid dehydrogenase 9001-67-6, Neuraminidase 9001-78-9 9001-99-4, RNase 9002-07-7, Trypsin 9004-07-3, Chymotrypsin 9004-10-8, Insulin, biological studies 9005-63-4D, Polyoxyethylene sorbitan, fatty acid esters 9016-45-9, Polyethylene glycol nonylphenyl ether 9035-74-9, Glycogen phosphorylase 10118-90-8, Minocycline 11111-12-9, Cephalosporins 13292-46-1, Rifampin 14271-04-6 14271-05-7 21645-51-2, Aluminum hydroxide, biological studies 22232-71-9, Mazindol 24730-10-7, Dihydroergocristine methanesulfonate 25953-19-9, Cefazoline 26780-50-7, Poly(lactide-co-glycolide) 30516-87-1 32986-56-4, Tobramycin 35189-28-7, Norgestimate 37517-28-5, Amikacin 53678-77-6, Muramyl dipeptide 53994-73-3, Cefaclor 55268-75-2, Cefuroxime 61036-62-2, Teicoplanin 64221-86-9, Imipenem 78110-38-0, Aztreonam 80738-43-8, Lincosamide 81103-11-9, Clarithromycin 82009-34-5, Cilastatin 82419-36-1, Ofloxacin 85721-33-1, Ciprofloxacin 123781-17-9, Histatin 189200-69-9, Polygen
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(therapeutic treatment and prevention of infections with bioactive materials encapsulated within biodegradable-biocompatible polymeric matrix)

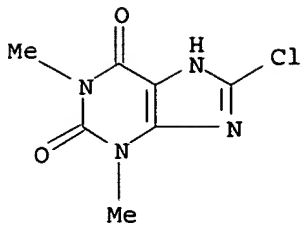
IT **523-87-5**, Dimenhydrinate
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(therapeutic treatment and prevention of infections with bioactive materials encapsulated within biodegradable-biocompatible polymeric matrix)

RN 523-87-5 HCAPLUS

CN 1H-Purine-2,6-dione, 8-chloro-3,7-dihydro-1,3-dimethyl-, compd. with 2-(diphenylmethoxy)-N,N-dimethylethanamine (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 85-18-7
CMF C7 H7 Cl N4 O2



CM 2

CRN 58-73-1
CMF C17 H21 N O

$Ph_2CH-O-CH_2-CH_2-NMe_2$

REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 2 OF 16 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:507701 HCAPLUS
DOCUMENT NUMBER: 135:107350
TITLE: Synthesis of purine derivatives and uses thereof (e.g. cyclin-dependent protein kinase inhibitors)
INVENTOR(S): Havlicek, Libor; Krystof, Vladimir; Siglerova, Vera; Lenobel, Rene; Van Onckelen, Henri; Berneman, Zwi Nisan; Slegers, Herman; Esmans, Edgard; Strnad, Miroslav; Vermeulen, Katrien
PATENT ASSIGNEE(S): Universitaire Instelling Antwerpen, Belg.; Ustav Experimentalni Botaniky Akademie Ved Ceske Re Bupliky
SOURCE: PCT Int. Appl., 120 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001049688	A1	20010712	WO 2001-EP150	20010108
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1244668	A1	20021002	EP 2001-907418	20010108
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				

PRIORITY APPLN. INFO.: EP 2000-200070 A 20000107
WO 2001-EP150 W 20010108
OTHER SOURCE(S): CASREACT 135:107350; MARPAT 135:107350

AB Title compds. I [Z = N or CH, provided that at most, one Z is CH; R6 = H, halo, NH2, OH, cycloalkyl (alkyl), etc.; R8 = H, halo, NH2, OH, carboxyl, CN, NO2, amido, sulfo, sulfamido, carbamino, (cyclo)alkyl, acyl, cycloalkyl, etc.; R2 = H, halo, amido, carbamino, carboxyl, sulfamido, alkyl, cycloalkyl (alkyl), aryl, heterocycle, etc.; R9 = H, alkyl, acyl, carboxyl, amido, sulfo, sulfamido, carbamino, cycloalkyl (alkyl), cycloheteroalkyl alkyl, etc.; wherein at least one of R2-9 is an amine substituted with a catechol or related group] are prepd. Examples include 4 general syntheses for over 100 compds. and 9 bioassays. For instance, 2-hydroxyethylamine was reacted with 2-chloro-9-isopropyl-6-[(1-phenyl-2-hydroxyethyl)amino]purine for 3 h at 160.degree.C to generate I (Z = N, R6 = (1-phenyl-2-hydroxyethyl)amino, R2 = 2-hydroxyethyl, R9 = i-Pr, R8 = H; II). I are inhibitors of cyclin-dependent kinases; II had IC50 = 1.4 .mu.M for p34cdc2. I also exhibited cytotoxicity in T-lymphoblastic leukemia cells, II had IC50 = 18 .mu.M and in B16 malanoma cells, II had IC50 = 19 .mu.M. Invention compds. are claimed for use as antiviral, antimitotic, antiproliferative immunomodulating, immunosuppressive, antiinflammatory, antimicrobial and antitumor agents.

IC ICM C07D473-34
ICS C07D473-40; A61K031-52; A61P035-00

CC 28-18 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1

ST purine cyclin dependent kinase inhibitor prepn; antimitotic antiviral antiproliferative **immunosuppressive** purine prepn; antitumor purine prepn

IT Affinity chromatographic stationary phases
Antitumor agents
Antiviral agents
Cyclin dependent kinase inhibitors
Immunomodulators
Immunosuppressants
(synthesis of purine derivs. and uses thereof (e.g. cyclin-dependent protein kinase inhibitors))

IT 19272-68-5P 113852-41-8P 158982-16-2P 182798-90-9P 184350-26-3P
185408-92-8P 189232-35-7P 189232-36-8P 189232-42-6P 349657-59-6P
349657-61-0P 349657-65-4P **349657-67-6P** **349657-69-8P**
349657-70-1P **349657-72-3P** **349657-74-5P**
349657-79-0P **349657-85-8P** 349657-93-8P 349658-00-0P
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349658-28-2P 349658-34-0P 349658-38-4P 349658-41-9P 349658-47-5P
349658-55-5P 349658-64-6P 349658-67-9P 349658-71-5P 349658-76-0P
349658-80-6P 349658-90-8P 349658-95-3P 349659-00-3P 349659-04-7P
349659-08-1P 349659-12-7P 349659-16-1P 349659-20-7P 349659-23-0P
349659-25-2P 349659-28-5P 349659-29-6P 349659-31-0P 349659-34-3P
349659-36-5P 349659-38-7P 349659-40-1P 349659-41-2P 349659-43-4P
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349659-58-1P 349659-62-7P **349659-66-1P** 349659-70-7P
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349659-99-0P 349660-00-0P 349660-01-1P 349660-02-2P 349660-03-3P
349660-04-4P 349660-05-5P 349660-06-6P 349660-07-7P 349660-08-8P
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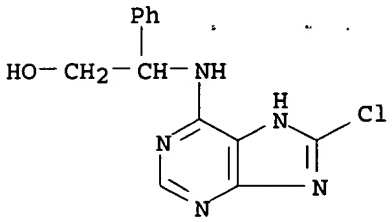
349660-19-1P 349660-20-4P 349660-21-5P 349660-22-6P 349660-23-7P
349660-24-8P 349660-25-9P 349660-26-0P 349660-27-1P 349660-28-2P
349660-29-3P 349660-30-6P 349660-31-7P **349660-32-8P**
349660-33-9P 349660-34-0P **349660-35-1P** 349660-36-2P
349660-37-3P 349660-38-4P 349660-39-5P 349660-40-8P 349660-41-9P
349660-42-0P 349660-43-1P 349660-44-2P 349660-45-3P 349660-46-4P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological

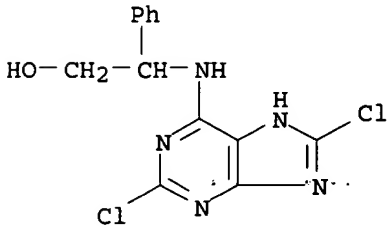
study, unclassified); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(synthesis of purine derivs. and uses thereof (e.g. cyclin-dependent protein kinase inhibitors))

IT **349657-67-6P 349657-69-8P 349657-72-3P**
349657-74-5P 349657-79-0P 349657-85-8P
349659-66-1P 349660-32-8P 349660-35-1P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(synthesis of purine derivs. and uses thereof (e.g. cyclin-dependent protein kinase inhibitors))

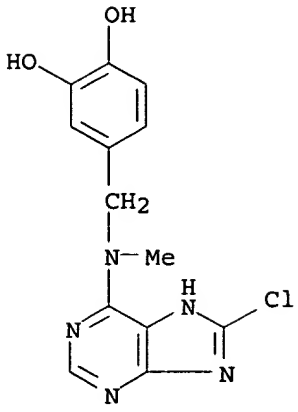
RN 349657-67-6 HCAPLUS
CN Benzeneethanol, .beta.-[(8-chloro-1H-purin-6-yl)amino]- (9CI) (CA INDEX NAME)



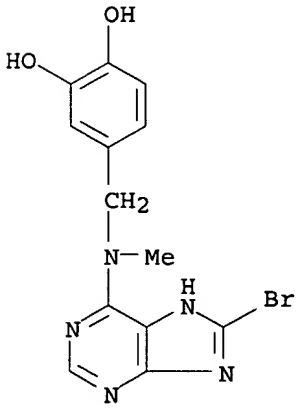
RN 349657-69-8 HCAPLUS
CN Benzeneethanol, .beta.-[(2,8-dichloro-1H-purin-6-yl)amino]- (9CI) (CA INDEX NAME)



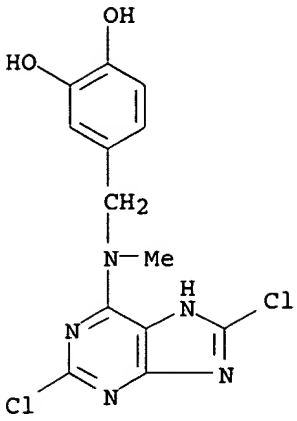
RN 349657-72-3 HCAPLUS
CN 1,2-Benzenediol, 4-[[(8-chloro-1H-purin-6-yl)methylamino]methyl]- (9CI) (CA INDEX NAME)



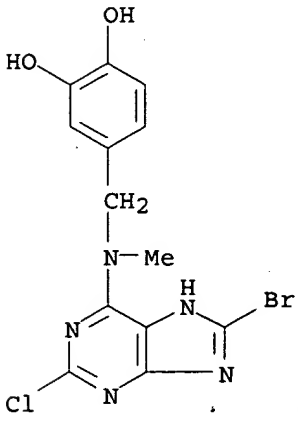
RN 349657-74-5 HCAPLUS
CN 1,2-Benzenediol, 4-[[(8-bromo-1H-purin-6-yl)methylamino]methyl]- (9CI) (CA INDEX NAME)



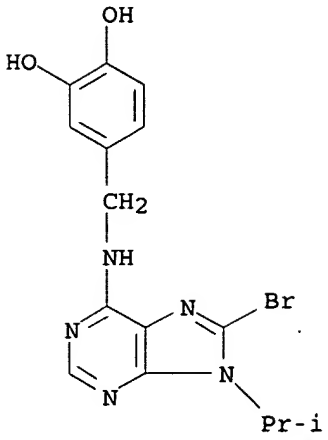
RN 349657-79-0 HCAPLUS
CN 1,2-Benzenediol, 4-[[(2,8-dichloro-1H-purin-6-yl)methylamino]methyl]- (9CI) (CA INDEX NAME)



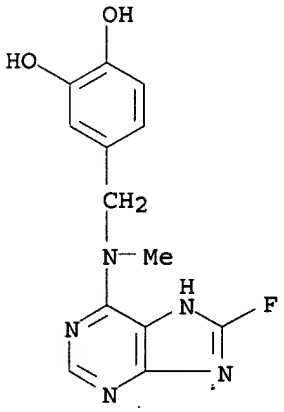
RN 349657-85-8 HCAPLUS
CN 1,2-Benzenediol, 4-[[(8-bromo-2-chloro-1H-purin-6-yl)methylamino]methyl]-
(9CI) (CA INDEX NAME)



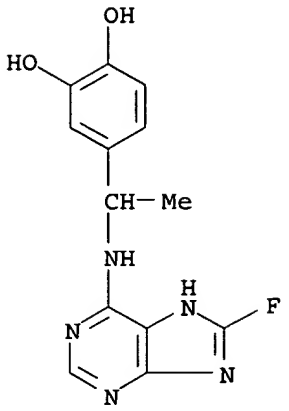
RN 349659-66-1 HCAPLUS
CN 1,2-Benzenediol, 4-[[[8-bromo-9-(1-methylethyl)-9H-purin-6-
yl]amino]methyl]- (9CI) (CA INDEX NAME)



RN 349660-32-8 HCAPLUS
CN 1,2-Benzenediol, 4-[[(8-fluoro-1H-purin-6-yl)methylamino]methyl]- (9CI) (CA INDEX NAME)



RN 349660-35-1 HCAPLUS
CN 1,2-Benzenediol, 4-[1-[(8-fluoro-1H-purin-6-yl)amino]ethyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 3 OF 16 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:167783 HCAPLUS
DOCUMENT NUMBER: 134:212734
TITLE: Oral dosage forms containing polymers and plasticizers
INVENTOR(S): Bartholomaeus, Johannes; Ziegler, Iris
PATENT ASSIGNEE(S): Gruenenthal G.m.b.H., Germany
SOURCE: PCT Int. Appl., 46 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001015667	A1	20010308	WO 2000-EP8402	20000829
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
DE 19940740	A1	20010301	DE 1999-19940740	19990831
DE 19940944	A1	20010315	DE 1999-19940944	19990831
DE 10023699	A1	20010419	DE 2000-10023699	20000516
EP 1207858	A1	20020529	EP 2000-964052	20000829
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
BR 2000013826	A	20020730	BR 2000-13826	20000829
NO 2002000939	A	20020422	NO 2002-939	20020226

PRIORITY APPLN. INFO.:
DE 1999-19940740 A 19990831
DE 1999-19940944 A 19990831
DE 2000-10023699 A 20000516
DE 1999-29923344 U1 19990831
DE 1999-29923345 U1 19990831
WO 2000-EP8402 W 20000829

AB The invention relates to oral dosage forms with controlled total-release of an active substance. The active substance is present in the form of at least 2 different salts that are present in the dosage form in a solid state of aggregation and the release of the substances in vitro occur differently. Tablets contained promethazine-HCl 15, another promethazine salt 39, microcryst. cellulose 120, HPMC 75, siO2 2.5 and Mg stearate 2.5 g.

IC ICM A61K009-22
ICS A61K009-52

CC 63-6 (Pharmaceuticals)

IT Adrenoceptor agonists
Aging, animal
Allergy inhibitors
Analgesics
Anthelmintics
Antiarrhythmics
Antiarteriosclerotics
Antiasthmatics
Antibiotics
Anticoagulants
Antidepressants
Antidiabetic agents
Antidotes
Antiemetics
Antihistamines
Antihypertensives
Antimigraine agents
Antiparkinsonian agents
Antipyretics
Antirheumatic agents
Antitumor agents
Antitussives
Antiviral agents
Anxiolytics
Beeswax
Bronchodilators
Choleretics
Cholinergic agonists
Cognition enhancers
Cytotoxic agents
Diuretics
Expectorants
Fungicides
Hemostatics
Hypnotics and Sedatives
Immunomodulators
Muscle relaxants
Nervous system stimulants
Nutrients
Plasticizers
Platelet aggregation inhibitors
Tuberculostatics
Vasodilators
(oral dosage forms contg. polymers and plasticizers)

IT 57-27-2, Morphine, biological studies 57-42-1, Pethidine 57-55-6, Propylene glycol, biological studies 58-33-3, Promethazine hydrochloride 60-87-7, Promethazine 62-67-9, Nalorphine 76-42-6, Oxycodone 76-57-3, Codeine 77-07-6, Levorphanol 77-89-4, Acetyl triethylcitrate 77-90-7, Acetyl tributylcitrate 77-92-9D, Citric acid, esters 77-93-0, Triethyl citrate 77-94-1, Tributyl citrate 84-66-2, Diethyl phthalate

84-74-2, Dibutyl phthalate 102-76-1, Triacetin 109-43-3, Dibutyl sebacate 110-40-7, Diethyl sebacate 112-80-1, Oleic acid, biological studies 125-28-0, Dihydrocodeine 125-29-1, Hydrocodone 125-58-6, Levomethadone 302-41-0, Piritramide 357-56-2, Dextromoramide 359-83-1, Pentazocine 437-38-7, Fentanyl 466-99-9, Hydromorphone 469-62-5, Dextropropoxyphene 469-79-4, Ketobemidone 561-27-3, Diacetylmorphine 915-30-0, Diphenoxylate 1406-18-4, Vitamine 9003-01-4, Poly(acrylic acid) 9003-20-7, Polyvinyl acetate 9003-39-8, PVP 9004-34-6D, Cellulose, derivates, biological studies 9004-35-7, Cellulose acetate 9004-38-0, Cellulose acetate phthalate 9004-57-3, Ethyl cellulose 9004-64-2, Hydroxypropyl cellulose 9004-65-3, Hydroxypropyl methyl cellulose 9010-88-2, Eudragit NE30D 14019-10-4 14521-96-1, Etorphine **17693-51-5** 18641-57-1, Compritol ATO 888 20594-83-6, Nalbuphine 21363-18-8, Viminol 25087-26-7, Polymethacrylic acid 25212-88-8, Eudragit L30D 25322-68-3, Polyethylene glycol 26936-24-3, Eudragit FS 27203-92-5, Tramadol 31566-31-1, Glycerin monostearate 33434-24-1, Eudragit RS 36282-47-0, Tramadol hydrochloride 37353-59-6, Hydroxymethyl cellulose 42408-82-2, Butorphanol 51822-44-7, Eudragit L 51931-66-9, Tilidine 52485-79-7, Buprenorphine 53648-55-8, Dezocine 54340-58-8, Meptazinol 56030-54-7, Sufentanil 59708-52-0, Carfentanil 61380-40-3, Lofentanil 62112-17-8, Fentathienil 71138-97-1, Hydroxypropyl methyl cellulose acetate succinate 71195-58-9, Alfentanil 101343-69-5, Ocfentanil 101345-71-5, Brifentanil 120656-74-8, Trefentanil 132875-61-7, Remifentanil 328062-82-4 328933-20-6

RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(oral dosage forms contg. polymers and plasticizers)

IT **17693-51-5**

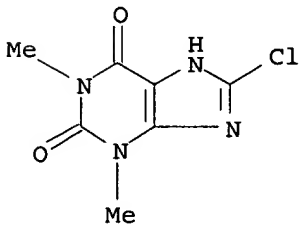
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(oral dosage forms contg. polymers and plasticizers)

RN 17693-51-5 HCAPLUS

CN 1H-Purine-2,6-dione, 8-chloro-3,7-dihydro-1,3-dimethyl-, compd. with N,N,.alpha.-trimethyl-10H-phenothiazine-10-ethanamine (1:1) (9CI) (CA INDEX NAME)

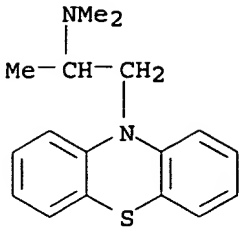
CM 1

CRN 85-18-7
CMF C7 H7 Cl N4 O2



CM 2

CRN 60-87-7
CMF C17 H20 N2 S



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 4 OF 16 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:513698 HCAPLUS
DOCUMENT NUMBER: 133:129894
TITLE: Substituted nitrogen heterocyclic derivatives and pharmaceutical use thereof
INVENTOR(S): Hanus, Jan; Krystof, Vladimir; Hajduch, Marian; Vesely, Jaroslav; Strnad, Miroslav
PATENT ASSIGNEE(S): Ustav Experimentalni Botaniky Av Cr, Czech Rep.; Lachema, A.S.
SOURCE: PCT Int. Appl., 89 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000043394	A1	20000727	WO 2000-CZ2	20000125
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1147108	A1	20011024	EP 2000-901478	20000125
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				

PRIORITY APPLN. INFO.: CZ 1999-273 A 19990126
WO 2000-CZ2 W 20000125
OTHER SOURCE(S): MARPAT 133:129894
AB Substituted nitrogen heterocyclic derivs. having cytostatic, anticancer, antimitotic, antineurogenerative, immunosuppressive and antimicrobial effects are provided. Also provided are methods for prepn. of these derivs., the use of the compds. as drugs, pharmaceutical compns. and combined pharmaceutical applications,, and the use of these derivs. for drug prodn. Compds. of the invention include e.g. 9-isopropylpurine derivs.
IC ICM C07D473-16
ICS C07D473-32; C07D473-34; C07D473-40; C07D487-04; A61K031-52; A61P035-00; C07D487-04; C07D239-00; C07D231-00; C07D487-04; C07D239-00; C07D209-00
CC 1-12 (Pharmacology)

Section cross-reference(s): 9, 28, 63

ST cytostatic antitumor antimitotic nitrogen heterocycle deriv; antineurogenerative **immunosuppressive** antimicrobial nitrogen heterocycle deriv; isopropylpurine deriv prepn therapeutic

IT Affinity chromatographic stationary phases
Animal tissue culture
Anti-Alzheimer's agents
Antidiabetic agents
Antimicrobial agents
Antirheumatic agents
Antitumor agents
Antiviral agents
Cardiovascular agents
Cytotoxic agents
Drug delivery systems
Fungicides
Gout
Human **immunodeficiency** virus 1
Human **immunodeficiency** virus 2
Immunoassay
Immunosuppressants
Lupus erythematosus
Murine sarcoma virus
Parasiticides
Psoriasis
Translation, genetic
Vaccines
(substituted nitrogen heterocyclic derivs., prepn., pharmaceutical compns., and therapeutic, diagnostic, and other uses)

IT **286406-69-7P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(prepn. and reaction; substituted nitrogen heterocyclic derivs., prepn., pharmaceutical compns., and therapeutic, diagnostic, and other uses)

IT 18203-85-5D, 9-Isopropylpurine, derivs. **286404-71-5**
286404-72-6 **286404-73-7** **286404-74-8**
286404-75-9 286404-76-0 286404-77-1 **286404-78-2**
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286405-70-7 **286405-72-9** **286405-73-0**
286405-74-1 286405-75-2 286405-76-3 **286405-77-4**
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RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BUU (Biological use, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(substituted nitrogen heterocyclic derivs., prepn., pharmaceutical compns., and therapeutic use)

IT 286406-70-0P **286406-71-1P** **286406-72-2P**
286406-74-4P **286406-76-6P** 286406-78-8P 286406-81-3P
286406-82-4P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BUU (Biological use, unclassified); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)

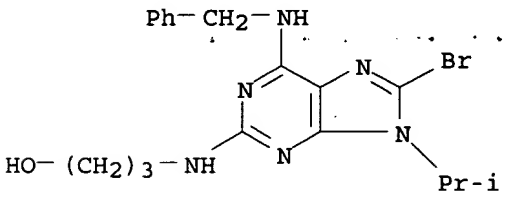
(substituted nitrogen heterocyclic derivs., prepn., pharmaceutical compns., and therapeutic, diagnostic, and other uses)

IT **286406-85-7P** 286406-86-8P 286406-87-9P **286406-88-0P**
286406-89-1P **286406-90-4P** 286406-91-5P 286406-92-6P
286406-93-7P **286406-94-8P** **286406-95-9P**
286406-97-1P 286406-98-2P 286406-99-3P **286407-00-9P**
286407-01-0P **286407-02-1P** **286407-03-2P**
286407-04-3P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(substituted nitrogen heterocyclic derivs., prepn., pharmaceutical compns., and therapeutic, diagnostic, and other uses)

IT 101622-51-9, Olomoucine 186692-46-6, Roscovitine 212844-53-6, Purvalanol A **286406-84-6** **286406-96-0**
286407-05-4 **286407-06-5** **286407-07-6**
286407-08-7 **286407-09-8** 286407-10-1
286407-11-2 **286407-12-3** **286407-13-4**
286407-14-5
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(substituted nitrogen heterocyclic derivs., prepn., pharmaceutical compns., and therapeutic, diagnostic, and other uses)

IT **286406-69-7P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(prepn. and reaction; substituted nitrogen heterocyclic derivs., prepn., pharmaceutical compns., and therapeutic, diagnostic, and other uses)

RN 286406-69-7 HCAPLUS
CN 1-Propanol, 3-[[8-bromo-9-(1-methylethyl)-6-[(phenylmethyl)amino]-9H-purin-2-yl]amino]- (9CI) (CA INDEX NAME)



IT **286404-71-5** **286404-73-7** **286404-74-8**
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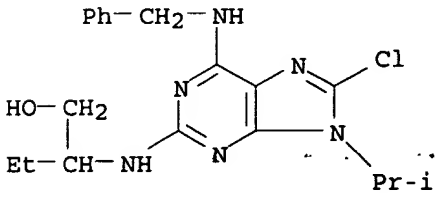
286405-66-1 286405-70-7 286405-72-9
286405-73-0 286405-74-1 286405-77-4
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BUU (Biological use, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(substituted nitrogen heterocyclic derivs., prepn., pharmaceutical compns., and therapeutic use)

RN 286404-71-5 HCAPLUS
CN 1-Butanol, 2-[[8-chloro-9-(1-methylethyl)-6-[(phenylmethyl)amino]-9H-purin-2-yl]amino]- (9CI) (CA INDEX NAME)



RN 286404-73-7 HCAPLUS
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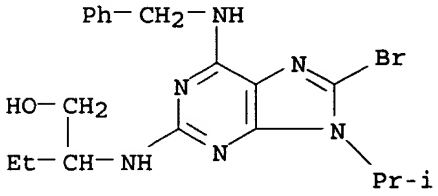
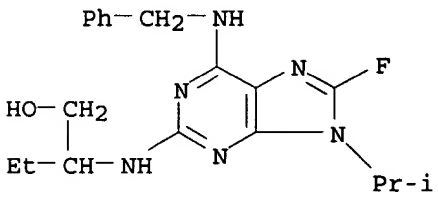
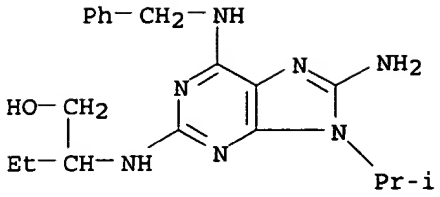


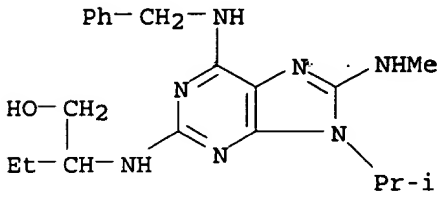
RN 286404-74-8 HCAPLUS
CN 1-Butanol, 2-[[8-fluoro-9-(1-methylethyl)-6-[(phenylmethyl)amino]-9H-purin-2-yl]amino]- (9CI) (CA INDEX NAME)



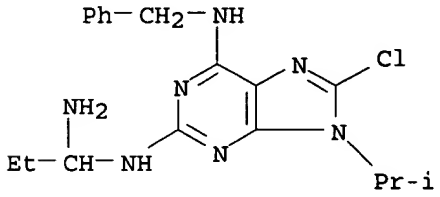
RN 286404-75-9 HCAPLUS
CN 1-Butanol, 2-[[8-amino-9-(1-methylethyl)-6-[(phenylmethyl)amino]-9H-purin-2-yl]amino]- (9CI) (CA INDEX NAME)



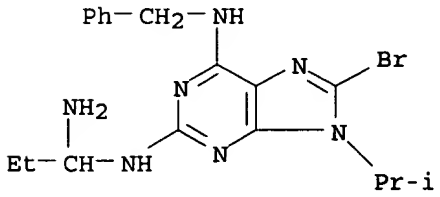
RN 286404-78-2 HCAPLUS
CN 1-Butanol, 2-[[8-(methylamino)-9-(1-methylethyl)-6-[(phenylmethyl)amino]-9H-purin-2-yl]amino]- (9CI) (CA INDEX NAME)



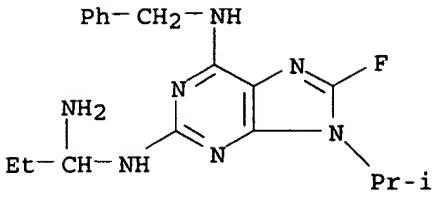
RN 286404-82-8 HCAPLUS
CN 9H-Purine-2,6-diamine, N2-(1-aminopropyl)-8-chloro-9-(1-methylethyl)-N6-(phenylmethyl)- (9CI) (CA INDEX NAME)



RN 286404-84-0 HCAPLUS
CN 9H-Purine-2,6-diamine, N2-(1-aminopropyl)-8-bromo-9-(1-methylethyl)-N6-(phenylmethyl)- (9CI) (CA INDEX NAME)



RN 286404-85-1 HCAPLUS
CN 9H-Purine-2,6-diamine, N2-(1-aminopropyl)-8-fluoro-9-(1-methylethyl)-N6-(phenylmethyl)- (9CI) (CA INDEX NAME)



RN 286404-86-2 HCAPLUS
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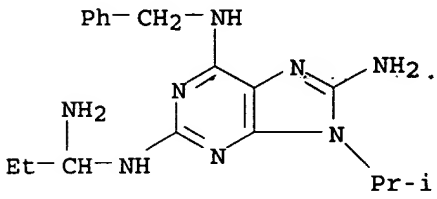
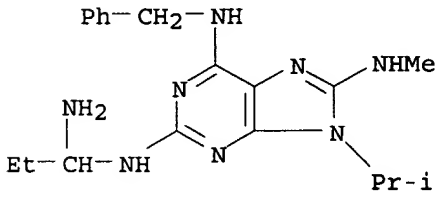
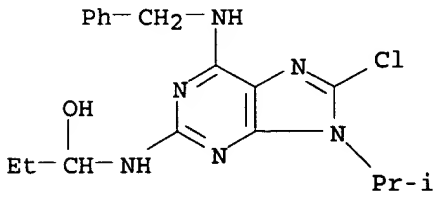


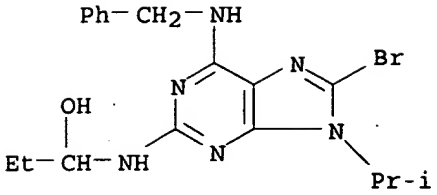
RN 286404-89-5 HCAPLUS
CN 9H-Purine-2,6,8-triamine, N2-(1-aminopropyl)-N8-methyl-9-(1-methylethyl)-N6-(phenylmethyl)- (9CI) (CA INDEX NAME)



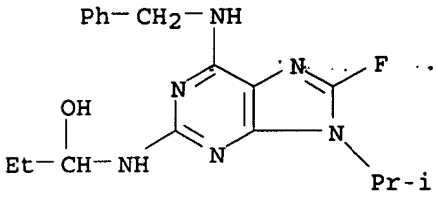
RN 286404-93-1 HCAPLUS
CN 1-Propanol, 1-[[8-chloro-9-(1-methylethyl)-6-[(phenylmethyl)amino]-9H-purin-2-yl]amino]- (9CI) (CA INDEX NAME)



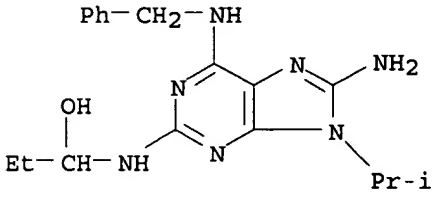
RN 286404-95-3 HCAPLUS
CN 1-Propanol, 1-[[8-bromo-9-(1-methylethyl)-6-[(phenylmethyl)amino]-9H-purin-2-yl]amino]- (9CI) (CA INDEX NAME)



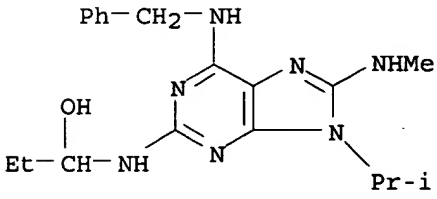
RN 286404-96-4 HCAPLUS
CN 1-Propanol, 1-[[8-fluoro-9-(1-methylethyl)-6-[(phenylmethyl)amino]-9H-purin-2-yl]amino]- (9CI) (CA INDEX NAME)



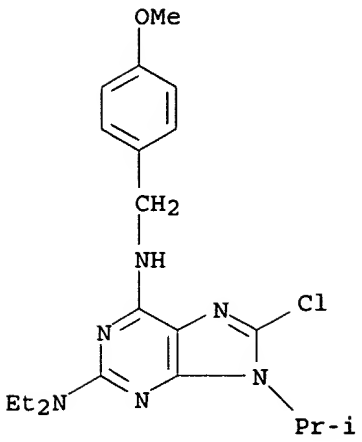
RN 286404-97-5 HCAPLUS
CN 1-Propanol, 1-[[8-amino-9-(1-methylethyl)-6-[(phenylmethyl)amino]-9H-purin-2-yl]amino]- (9CI) (CA INDEX NAME)



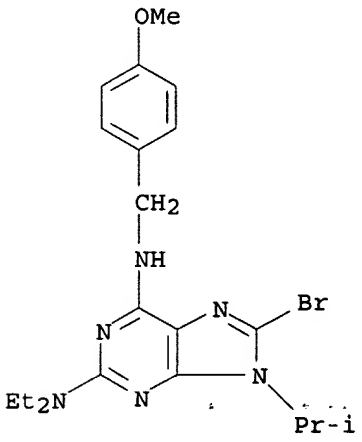
RN 286405-00-3 HCAPLUS
CN 1-Propanol, 1-[[8-(methylamino)-9-(1-methylethyl)-6-[(phenylmethyl)amino]-9H-purin-2-yl]amino]- (9CI) (CA INDEX NAME)



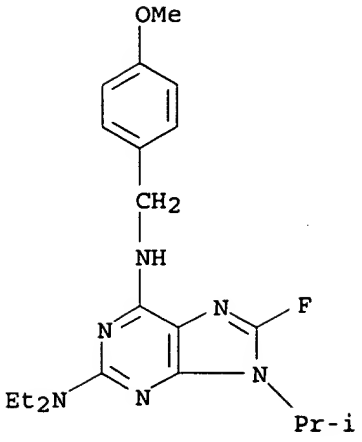
RN 286405-04-7 HCAPLUS
CN 9H-Purine-2,6-diamine, 8-chloro-N2,N2-diethyl-N6-[(4-methoxyphenyl)methyl]-9-(1-methylethyl)- (9CI) (CA INDEX NAME)



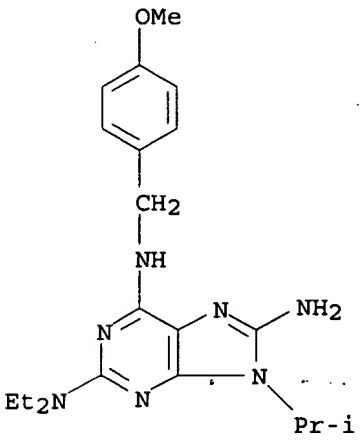
RN 286405-06-9 HCAPLUS
CN 9H-Purine-2,6-diamine, 8-bromo-N2,N2-diethyl-N6-[(4-methoxyphenyl)methyl]-9-(1-methylethyl)- (9CI) (CA INDEX NAME)



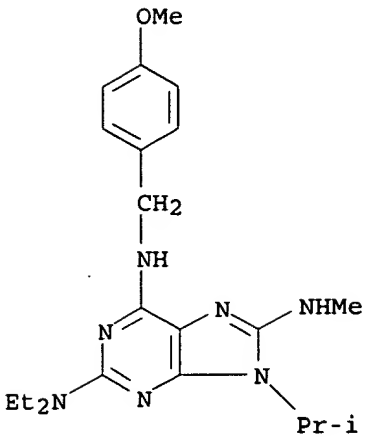
RN 286405-07-0 HCAPLUS
CN 9H-Purine-2,6-diamine, N2,N2-diethyl-8-fluoro-N6-[(4-methoxyphenyl)methyl]-9-(1-methylethyl)- (9CI) (CA INDEX NAME)



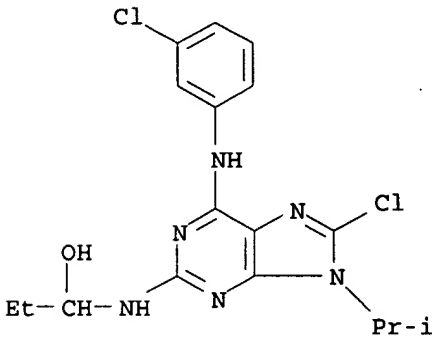
RN 286405-08-1 HCAPLUS
CN 9H-Purine-2,6,8-triamine, N2,N2-diethyl-N6-[(4-methoxyphenyl)methyl]-9-(1-methylethyl)- (9CI) (CA INDEX NAME)



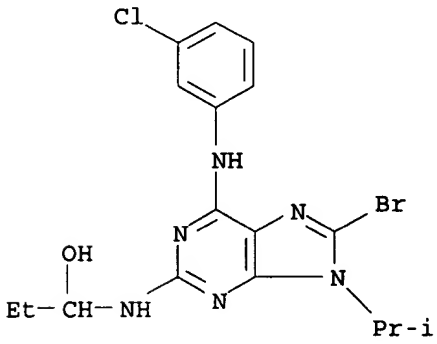
RN 286405-11-6 HCAPLUS
CN 9H-Purine-2,6,8-triamine, N2,N2-diethyl-N6-[(4-methoxyphenyl)methyl]-N8-methyl-9-(1-methylethyl)- (9CI) (CA INDEX NAME)



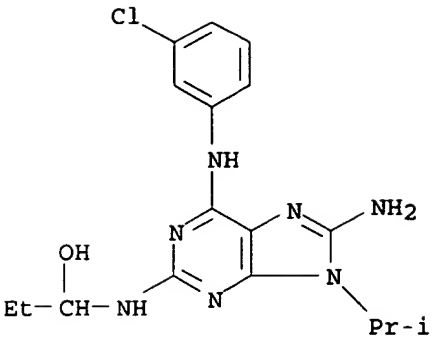
RN 286405-15-0 HCAPLUS
CN 1-Propanol, 1-[[8-chloro-6-[(3-chlorophenyl)amino]-9-(1-methylethyl)-9H-purin-2-yl]amino]- (9CI) (CA INDEX NAME)



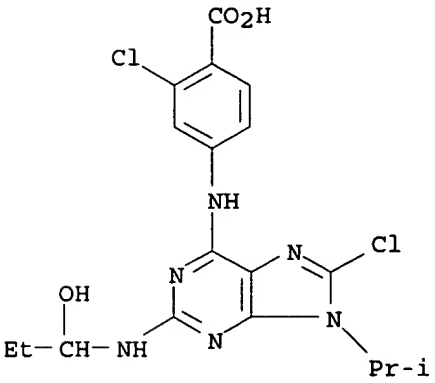
RN 286405-17-2 HCAPLUS
CN 1-Propanol, 1-[[8-bromo-6-[(3-chlorophenyl)amino]-9-(1-methylethyl)-9H-purin-2-yl]amino]- (9CI) (CA INDEX NAME)



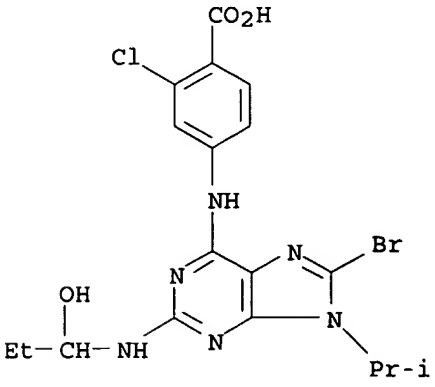
RN 286405-18-3 HCAPLUS
CN 1-Propanol, 1-[[8-amino-6-[(3-chlorophenyl)amino]-9-(1-methylethyl)-9H-purin-2-yl]amino]- (9CI) (CA INDEX NAME)



RN 286405-26-3 HCAPLUS
CN Benzoic acid, 2-chloro-4-[[8-chloro-2-[(1-hydroxypropyl)amino]-9-(1-methylethyl)-9H-purin-6-yl]amino]- (9CI) (CA INDEX NAME)

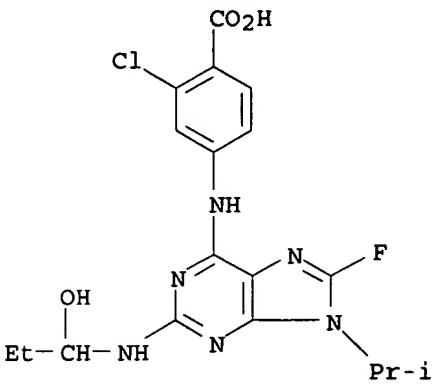


RN 286405-28-5 HCAPLUS
CN Benzoic acid, 4-[[8-bromo-2-[(1-hydroxypropyl)amino]-9-(1-methylethyl)-9H-purin-6-yl]amino]-2-chloro- (9CI) (CA INDEX NAME)

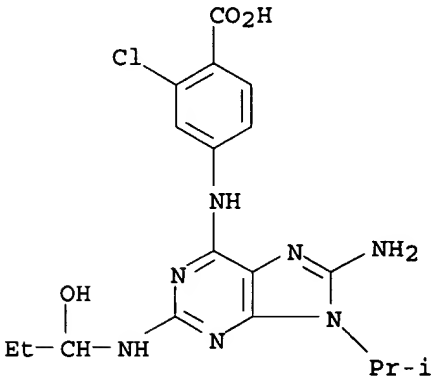


RN 286405-29-6 HCAPLUS
CN Benzoic acid, 2-chloro-4-[[8-fluoro-2-[(1-hydroxypropyl)amino]-9-(1-

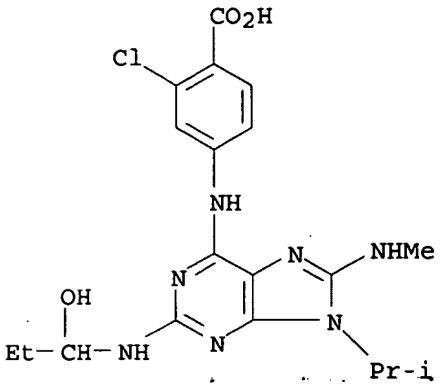
methylethyl)-9H-purin-6-yl]amino]- (9CI) (CA INDEX NAME)



RN 286405-30-9 HCAPLUS
CN Benzoic acid, 4-[[8-amino-2-[(1-hydroxypropyl)amino]-9-(1-methylethyl)-9H-purin-6-yl]amino]-2-chloro- (9CI) (CA INDEX NAME)

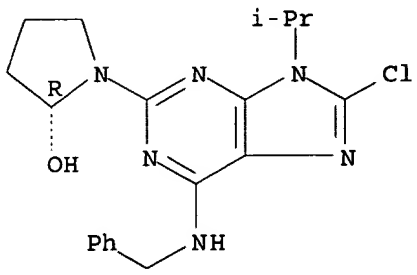


RN 286405-33-2 HCAPLUS
CN Benzoic acid, 2-chloro-4-[[2-[(1-hydroxypropyl)amino]-8-(methylamino)-9-(1-methylethyl)-9H-purin-6-yl]amino]- (9CI) (CA INDEX NAME)



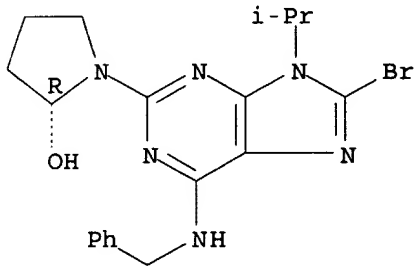
RN 286405-37-6 HCAPLUS
CN 2-Pyrrolidinol, 1-[8-chloro-9-(1-methylethyl)-6-[(phenylmethyl)amino]-9H-purin-2-yl]-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



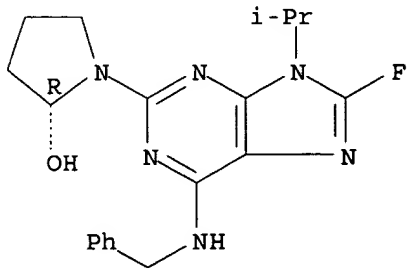
RN 286405-39-8 HCAPLUS
CN 2-Pyrrolidinol, 1-[8-bromo-9-(1-methylethyl)-6-[(phenylmethyl)amino]-9H-purin-2-yl]-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



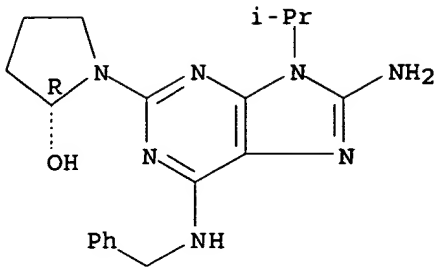
RN 286405-40-1 HCAPLUS
CN 2-Pyrrolidinol, 1-[8-fluoro-9-(1-methylethyl)-6-[(phenylmethyl)amino]-9H-purin-2-yl]-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



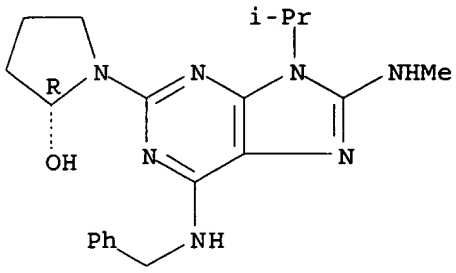
RN 286405-41-2 HCAPLUS
CN 2-Pyrrolidinol, 1-[8-amino-9-(1-methylethyl)-6-[(phenylmethyl)amino]-9H-purin-2-yl]-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



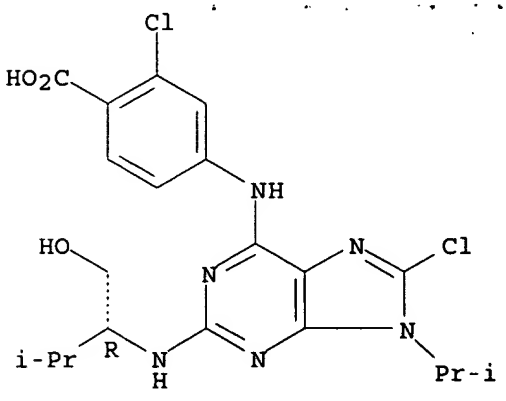
RN 286405-44-5 HCAPLUS
CN 2-Pyrrolidinol, 1-[8-(methylamino)-9-(1-methylethyl)-6-[(phenylmethyl)amino]-9H-purin-2-yl]-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



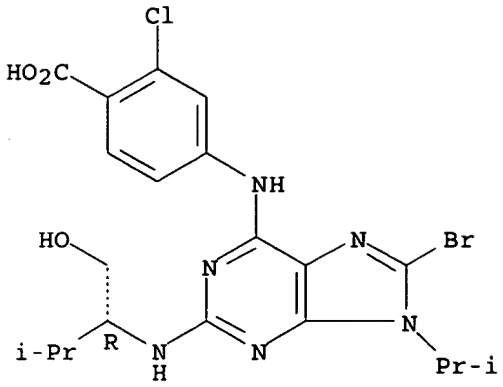
RN 286405-48-9 HCAPLUS
CN Benzoic acid, 2-chloro-4-[[8-chloro-2-[[(1R)-1-(hydroxymethyl)-2-methylpropyl]amino]-9-(1-methylethyl)-9H-purin-6-yl]amino]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



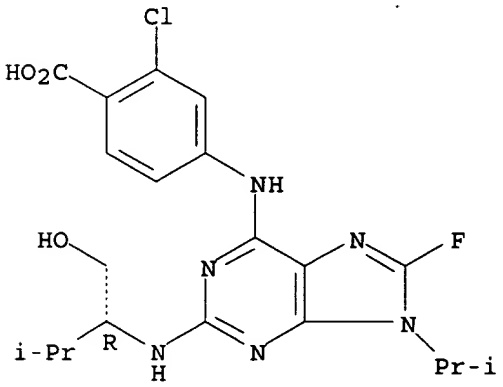
RN 286405-50-3 HCAPLUS
CN Benzoic acid, 4-[[8-bromo-2-[[(1R)-1-(hydroxymethyl)-2-methylpropyl]amino]-9-(1-methylethyl)-9H-purin-6-yl]amino]-2-chloro- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



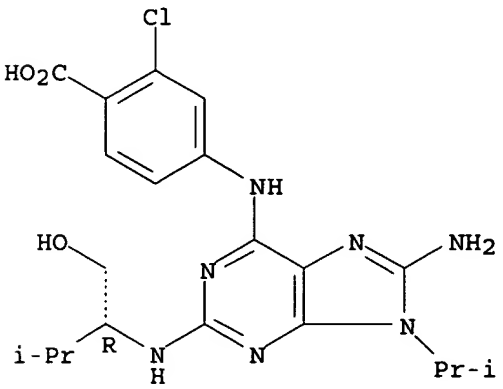
RN 286405-51-4 HCAPLUS
CN Benzoic acid, 2-chloro-4-[[8-fluoro-2-[[(1R)-1-(hydroxymethyl)-2-methylpropyl]amino]-9-(1-methylethyl)-9H-purin-6-yl]amino]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



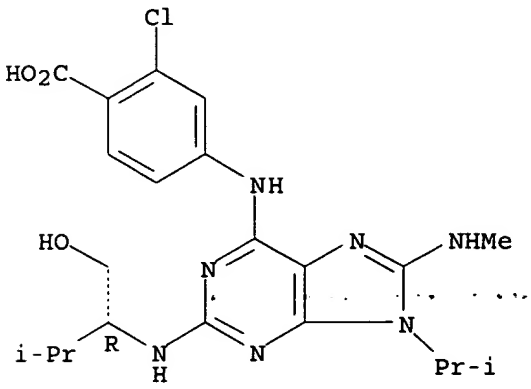
RN 286405-52-5 HCAPLUS
CN Benzoic acid, 4-[[8-amino-2-[[(1R)-1-(hydroxymethyl)-2-methylpropyl]amino]-9-(1-methylethyl)-9H-purin-6-yl]amino]-2-chloro- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



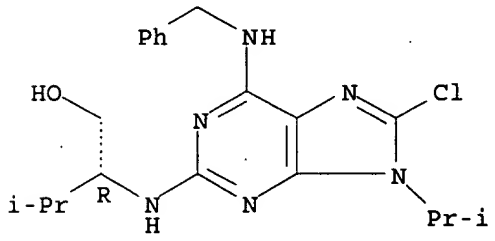
RN 286405-55-8 HCAPLUS
CN Benzoic acid, 2-chloro-4-[[2-[[(1R)-1-(hydroxymethyl)-2-methylpropyl]amino]-8-(methylamino)-9-(1-methylethyl)-9H-purin-6-yl]amino]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



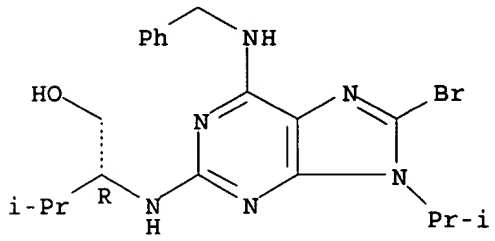
RN 286405-59-2 HCAPLUS
CN 1-Butanol, 2-[[8-chloro-9-(1-methylethyl)-6-[(phenylmethyl)amino]-9H-purin-2-yl]amino]-3-methyl-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 286405-61-6 HCAPLUS
CN 1-Butanol, 2-[[8-bromo-9-(1-methylethyl)-6-[(phenylmethyl)amino]-9H-purin-2-yl]amino]-3-methyl-, (2R)- (9CI) (CA INDEX NAME)

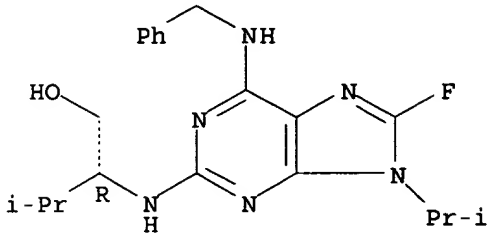
Absolute stereochemistry.



RN 286405-62-7 HCAPLUS
CN 1-Butanol, 2-[[8-fluoro-9-(1-methylethyl)-6-[(phenylmethyl)amino]-9H-purin-

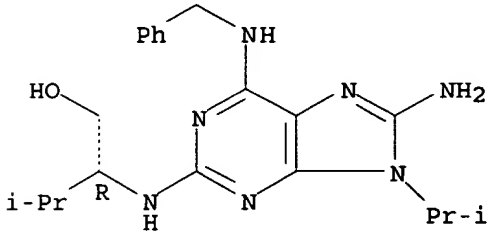
2-yl]amino]-3-methyl-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



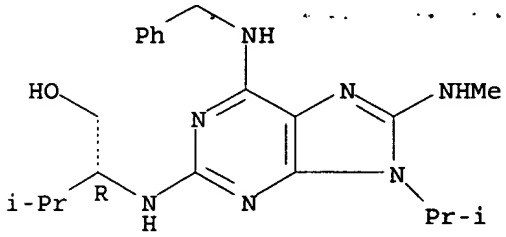
RN 286405-63-8 HCAPLUS
CN 1-Butanol, 2-[[8-amino-9-(1-methylethyl)-6-[(phenylmethyl)amino]-9H-purin-2-yl]amino]-3-methyl-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



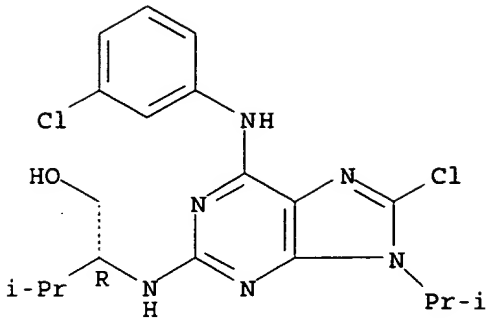
RN 286405-66-1 HCAPLUS
CN 1-Butanol, 3-methyl-2-[[8-(methylamino)-9-(1-methylethyl)-6-[(phenylmethyl)amino]-9H-purin-2-yl]amino]-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



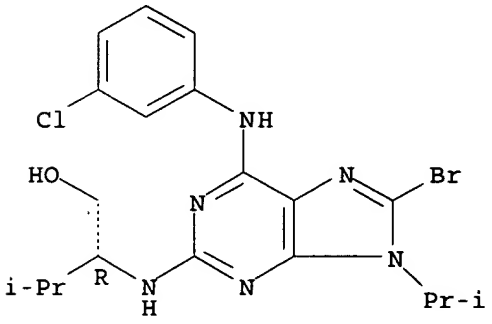
RN 286405-70-7 HCAPLUS
CN 1-Butanol, 2-[[8-chloro-6-[(3-chlorophenyl)amino]-9-(1-methylethyl)-9H-purin-2-yl]amino]-3-methyl-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



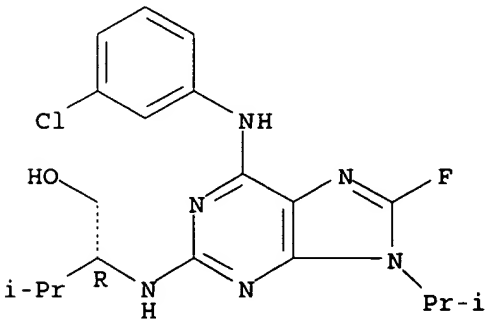
RN 286405-72-9 HCAPLUS
CN 1-Butanol, 2-[[8-bromo-6-[(3-chlorophenyl)amino]-9-(1-methylethyl)-9H-purin-2-yl]amino]-3-methyl-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



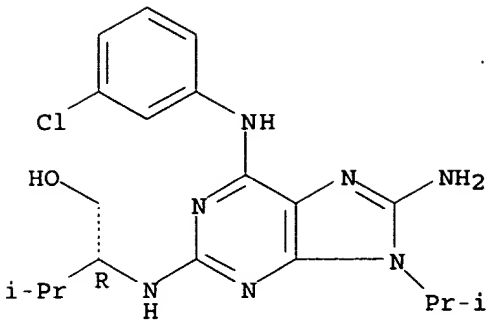
RN 286405-73-0 HCAPLUS
CN 1-Butanol, 2-[[6-[(3-chlorophenyl)amino]-8-fluoro-9-(1-methylethyl)-9H-purin-2-yl]amino]-3-methyl-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



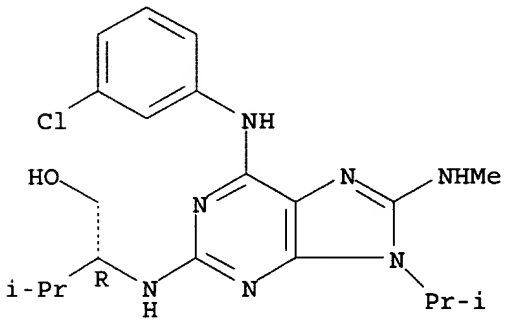
RN 286405-74-1 HCAPLUS
CN 1-Butanol, 2-[[8-amino-6-[(3-chlorophenyl)amino]-9-(1-methylethyl)-9H-purin-2-yl]amino]-3-methyl-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

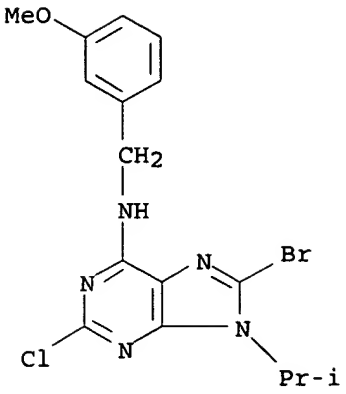


RN 286405-77-4 HCAPLUS
CN 1-Butanol, 2-[[6-[(3-chlorophenyl)amino]-8-(methylamino)-9-(1-methylethyl)-9H-purin-2-yl]amino]-3-methyl-, (2R)- (9CI) (CA INDEX NAME)

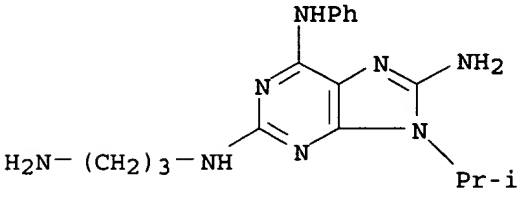
Absolute stereochemistry.



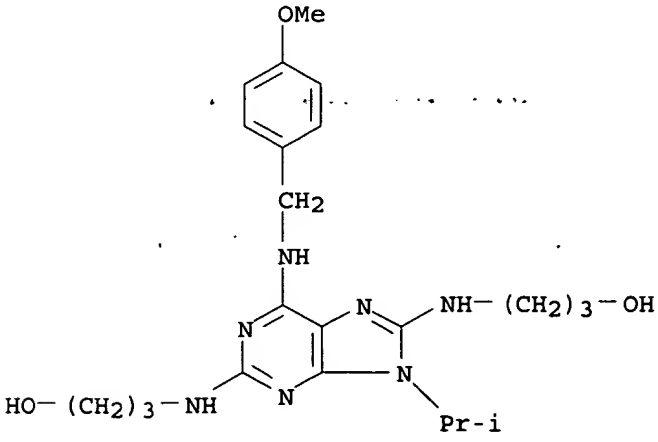
IT **286406-71-1P 286406-72-2P 286406-74-4P**
286406-76-6P 286406-82-4P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BUU (Biological use, unclassified); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(substituted nitrogen heterocyclic derivs., prepn., pharmaceutical compns., and therapeutic, diagnostic, and other uses)
RN 286406-71-1 HCAPLUS
CN 9H-Purin-6-amine, 8-bromo-2-chloro-N-[(3-methoxyphenyl)methyl]-9-(1-methylethyl)- (9CI) (CA INDEX NAME)



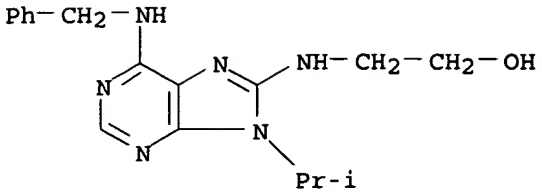
RN 286406-72-2 HCAPLUS
CN 9H-Purine-2,6,8-triamine, N2-(3-aminopropyl)-9-(1-methylethyl)-N6-phenyl- (9CI) (CA INDEX NAME)



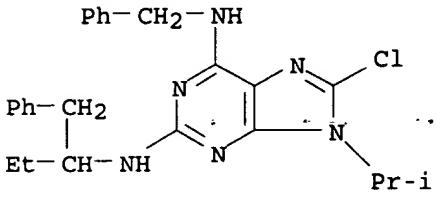
RN 286406-74-4 HCAPLUS
CN 1-Propanol, 3,3'-[[6-[[(4-methoxyphenyl)methyl]amino]-9-(1-methylethyl)-9H-purine-2,8-diyl]diimino]bis- (9CI) (CA INDEX NAME)



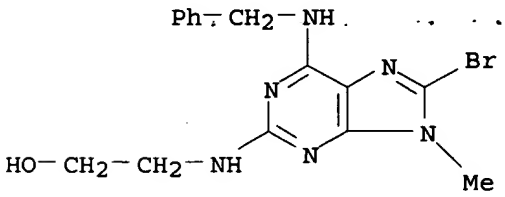
RN 286406-76-6 HCAPLUS
CN Ethanol, 2-[[9-(1-methylethyl)-6-[(phenylmethyl)amino]-9H-purin-8-yl]amino]- (9CI) (CA INDEX NAME)



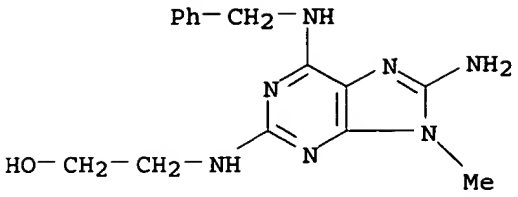
RN 286406-82-4 HCAPLUS
CN 9H-Purine-2,6-diamine, 8-chloro-9-(1-methylethyl)-N6-(phenylmethyl)-N2-[1-(phenylmethyl)propyl]- (9CI) (CA INDEX NAME)



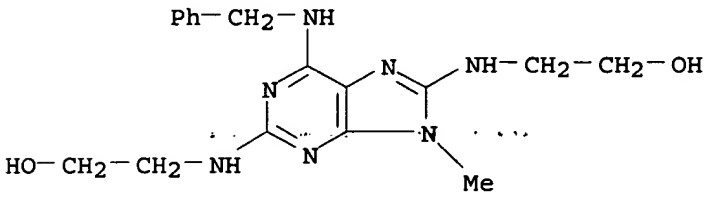
IT **286406-85-7P 286406-88-0P 286406-89-1P**
286406-90-4P 286406-93-7P 286406-94-8P
286406-95-9P 286406-97-1P 286407-00-9P
286407-01-0P 286407-02-1P 286407-03-2P
286407-04-3P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(substituted nitrogen heterocyclic derivs., prepn., pharmaceutical compns., and therapeutic, diagnostic, and other uses)
RN 286406-85-7 HCAPLUS
CN Ethanol, 2-[[8-bromo-9-methyl-6-[(phenylmethyl)amino]-9H-purin-2-yl]amino]- (9CI) (CA INDEX NAME)



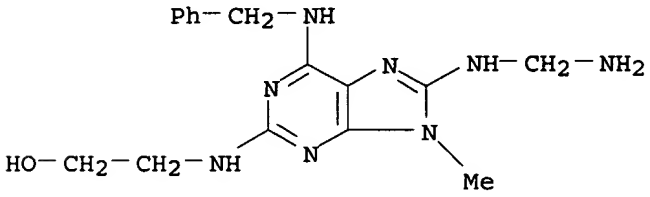
RN 286406-88-0 HCAPLUS
CN Ethanol, 2-[[8-amino-9-methyl-6-[(phenylmethyl)amino]-9H-purin-2-yl]amino]- (9CI) (CA INDEX NAME)



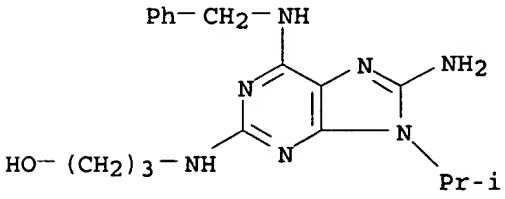
RN 286406-89-1 HCAPLUS
CN Ethanol, 2,2'-[[9-methyl-6-[(phenylmethyl)amino]-9H-purine-2,8-diyl]diimino]bis- (9CI) (CA INDEX NAME)



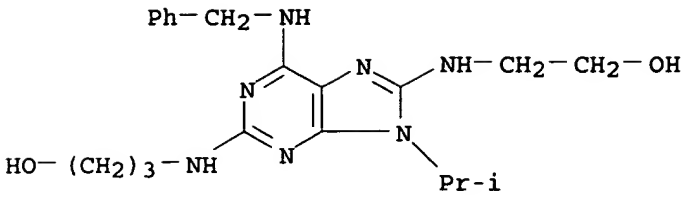
RN 286406-90-4 HCAPLUS
CN Ethanol, 2-[[8-[(aminomethyl)amino]-9-methyl-6-[(phenylmethyl)amino]-9H-purin-2-yl]amino]- (9CI) (CA INDEX NAME)



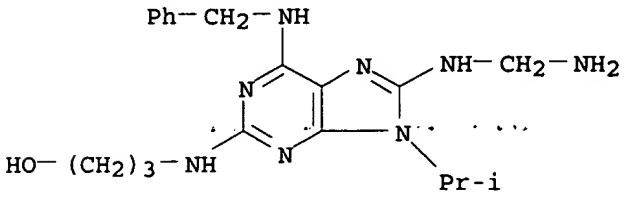
RN 286406-93-7 HCAPLUS
CN 1-Propanol, 3-[[8-amino-9-(1-methylethyl)-6-[(phenylmethyl)amino]-9H-purin-2-yl]amino]- (9CI) (CA INDEX NAME)



RN 286406-94-8 HCAPLUS
CN 1-Propanol, 3-[[8-[(2-hydroxyethyl)amino]-9-(1-methylethyl)-6-[(phenylmethyl)amino]-9H-purin-2-yl]amino]- (9CI) (CA INDEX NAME)

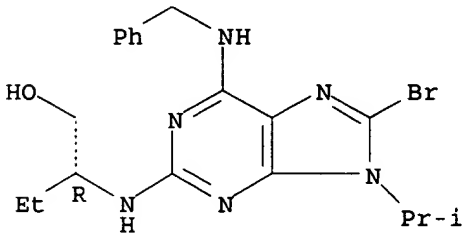


RN 286406-95-9 HCAPLUS
CN 1-Propanol, 3-[[8-[(aminomethyl)amino]-9-(1-methylethyl)-6-[(phenylmethyl)amino]-9H-purin-2-yl]amino]- (9CI) (CA INDEX NAME)



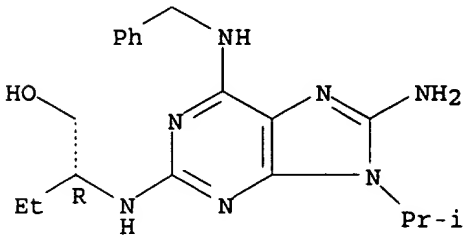
RN 286406-97-1 HCAPLUS
CN 1-Butanol, 2-[[8-bromo-9-(1-methylethyl)-6-[(phenylmethyl)amino]-9H-purin-2-yl]amino]-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 286407-00-9 HCAPLUS
CN 1-Butanol, 2-[[8-amino-9-(1-methylethyl)-6-[(phenylmethyl)amino]-9H-purin-2-yl]amino]-, (2R)- (9CI) (CA INDEX NAME)

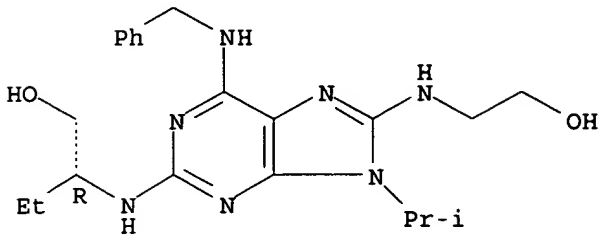
Absolute stereochemistry.



RN 286407-01-0 HCAPLUS
CN 1-Butanol, 2-[[8-[(2-hydroxyethyl)amino]-9-(1-methylethyl)-6-

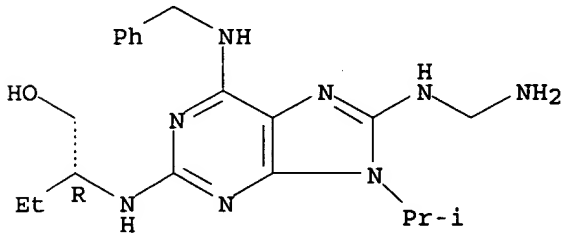
[(phenylmethyl)amino]-9H-purin-2-yl]amino]-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



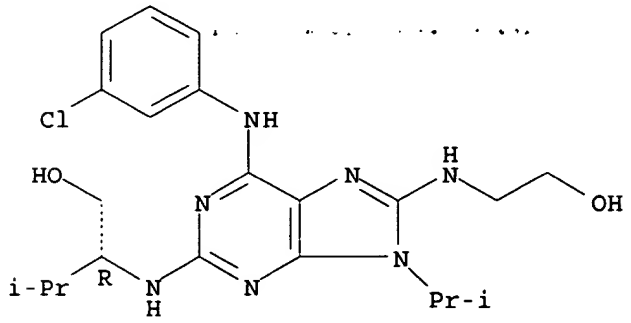
RN 286407-02-1 HCAPLUS
CN 1-Butanol, 2-[[8-[(aminomethyl)amino]-9-(1-methylethyl)-6-[(phenylmethyl)amino]-9H-purin-2-yl]amino]-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



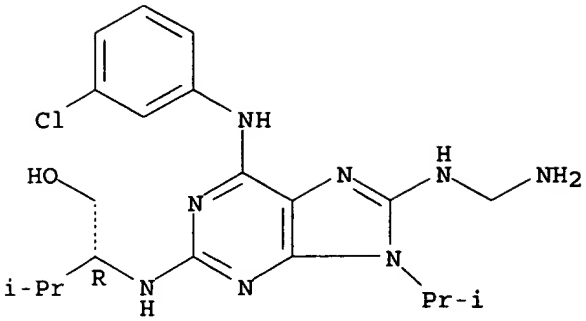
RN 286407-03-2 HCAPLUS
CN 1-Butanol, 2-[[6-[(3-chlorophenyl)amino]-8-[(2-hydroxyethyl)amino]-9-(1-methylethyl)-9H-purin-2-yl]amino]-3-methyl-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



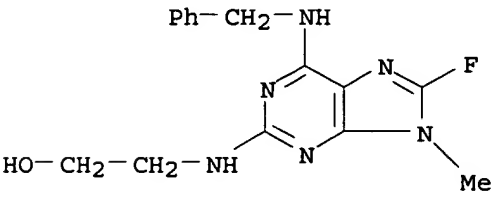
RN 286407-04-3 HCAPLUS
CN 1-Butanol, 2-[[8-[(aminomethyl)amino]-6-[(3-chlorophenyl)amino]-9-(1-methylethyl)-9H-purin-2-yl]amino]-3-methyl-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



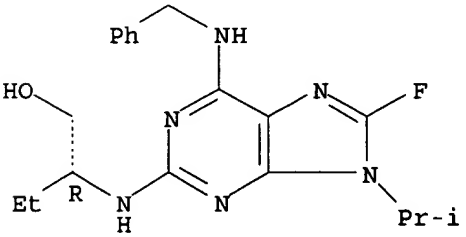
IT **286406-84-6 286406-96-0 286407-05-4**
286407-06-5 286407-07-6 286407-08-7
286407-09-8 286407-11-2 286407-12-3
286407-13-4 286407-14-5
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(substituted nitrogen heterocyclic derivs., prepn., pharmaceutical compns., and therapeutic, diagnostic, and other uses)

RN 286406-84-6 HCAPLUS
CN Ethanol, 2-[[8-fluoro-9-methyl-6-[(phenylmethyl)amino]-9H-purin-2-yl]amino]- (9CI) (CA INDEX NAME)

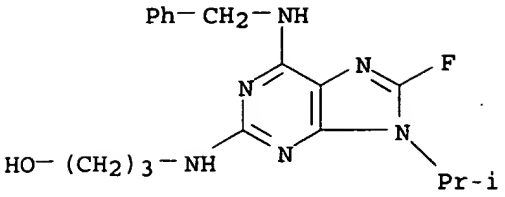


RN 286406-96-0 HCAPLUS
CN 1-Butanol, 2-[[8-fluoro-9-(1-methylethyl)-6-[(phenylmethyl)amino]-9H-purin-2-yl]amino]-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

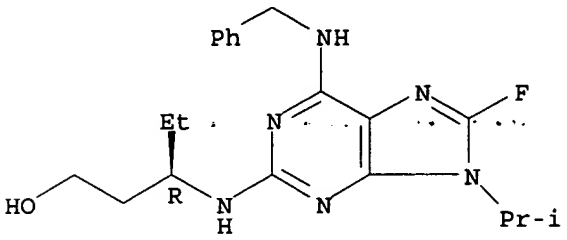


RN 286407-05-4 HCAPLUS
CN 1-Propanol, 3-[[8-fluoro-9-(1-methylethyl)-6-[(phenylmethyl)amino]-9H-purin-2-yl]amino]- (9CI) (CA INDEX NAME)



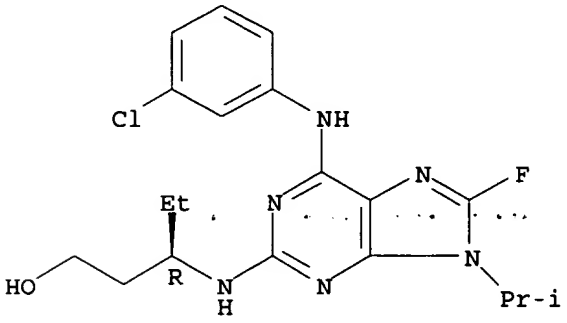
RN 286407-06-5 HCAPLUS
CN 1-Pentanol, 3-[[8-fluoro-9-(1-methylethyl)-6-[(phenylmethyl)amino]-9H-purin-2-yl]amino]-, (3R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



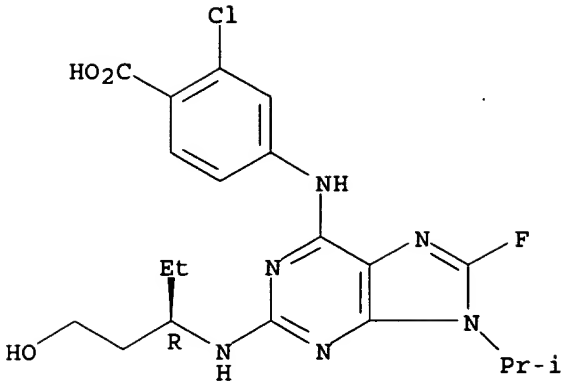
RN 286407-07-6 HCAPLUS
CN 1-Pentanol, 3-[[6-[(3-chlorophenyl)amino]-8-fluoro-9-(1-methylethyl)-9H-purin-2-yl]amino]-, (3R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



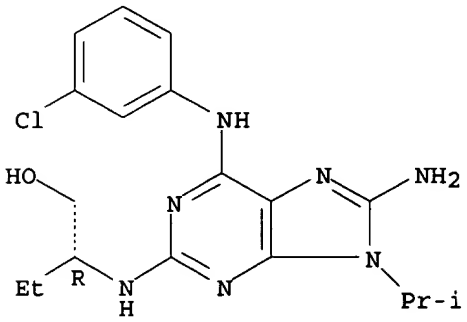
RN 286407-08-7 HCAPLUS
CN Benzoic acid, 2-chloro-4-[[2-[[(1R)-1-ethyl-3-hydroxypropyl]amino]-8-fluoro-9-(1-methylethyl)-9H-purin-6-yl]amino]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

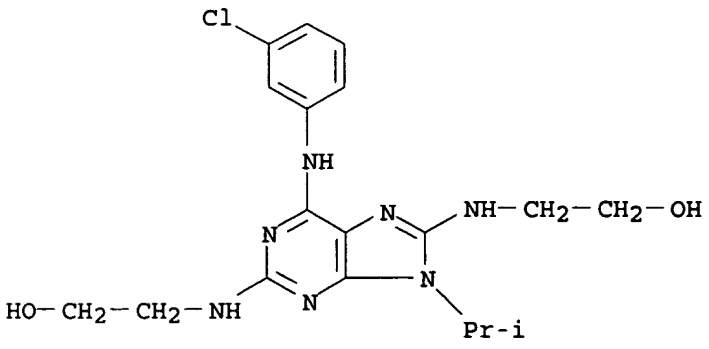


RN 286407-09-8 HCAPLUS
CN 1-Butanol, 2-[[8-amino-6-[(3-chlorophenyl)amino]-9-(1-methylethyl)-9H-purin-2-yl]amino]-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

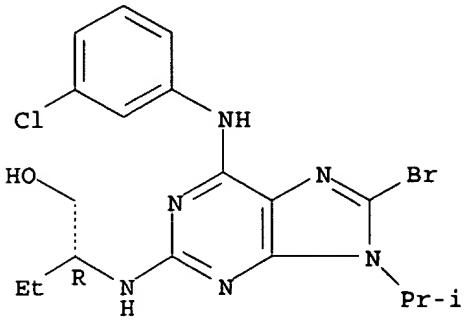


RN 286407-11-2 HCAPLUS
CN Ethanol, 2,2'-[[6-[(3-chlorophenyl)amino]-9-(1-methylethyl)-9H-purine-2,8-diyl]diimino]bis- (9CI) (CA INDEX NAME)



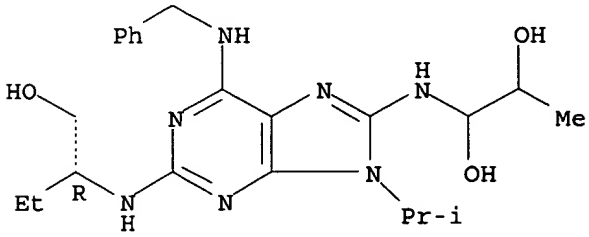
RN 286407-12-3 HCAPLUS
CN 1-Butanol, 2-[[8-bromo-6-[(3-chlorophenyl)amino]-9-(1-methylethyl)-9H-purin-2-yl]amino]-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



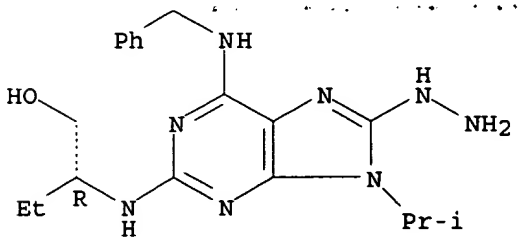
RN 286407-13-4 HCAPLUS
CN 1,2-Propanediol, 1-[[2-[[(1R)-1-(hydroxymethyl)propyl]amino]-9-(1-methylethyl)-6-[(phenylmethyl)amino]-9H-purin-8-yl]amino]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 286407-14-5 HCAPLUS
CN 8H-Purin-8-one, 7,9-dihydro-2-[[(1R)-1-(hydroxymethyl)propyl]amino]-9-(1-methylethyl)-6-[(phenylmethyl)amino]-, hydrazone (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 5 OF 16 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:655845 HCAPLUS
DOCUMENT NUMBER: 131:291269
TITLE: In vivo binding pair pretargeting with antibodies and methotrexate analogs
INVENTOR(S): Pomato, Nicholas; McCabe, Richard P.; Hawkins, Gregory

A.; Bredehorst, Reinhard; Kim, Chong-Ho; Vogel, Carl-Wilhelm
PATENT ASSIGNEE(S): Perimmune Holdings, Inc., USA
SOURCE: U.S., 76 pp., Cont.-in-part of U.S. 5,578,289.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

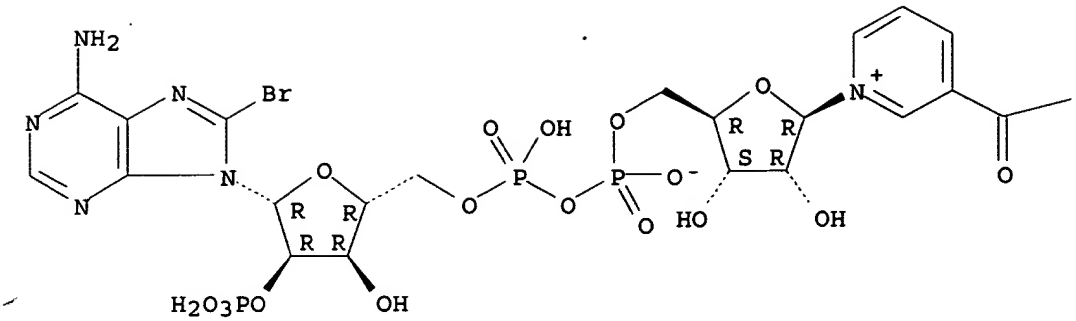
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5965106	A	19991012	US 1995-461267	19950605
US 5578289	A	19961126	US 1993-140186	19931104
PRIORITY APPLN. INFO.:			US 1992-846453	19920304
			US 1993-140186	19931104
			WO 1993-US1858	19930303

AB A method for in-vivo targeting a functional moiety in a patient by administering a targeting moiety coupled to an affinity component, wherein the targeting moiety has affinity for binding sites in a target area, and administering a binding partner to the affinity component coupled to a functional moiety to localize the functional moiety in the target area is disclosed. Preferably the targeting moiety is an antibody and the functional moiety is a radiometal when performing in vivo imaging or therapy. The affinity component may be a novel methotrexate analog. Preferably, the affinity component is thermo-stabilized.

IC ICM A61K039-395
ICS A61K051-00; A61K051-10
NCL 424001530
CC 63-5 (Pharmaceuticals)
Section cross-reference(s): 1, 15
IT **Immunoglobulins**
RL: RCT (Reactant); RACT (Reactant or reagent)
(M; in vivo binding pair pretargeting with antibodies and methotrexate analogs)
IT **62828-70-0P 246154-60-9P 246154-61-0P 246154-62-1P**
RL: RCT (Reactant); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(in vivo binding pair pretargeting with antibodies and methotrexate analogs)
IT **62828-70-0P 246154-60-9P 246154-61-0P 246154-62-1P**
RL: RCT (Reactant); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(in vivo binding pair pretargeting with antibodies and methotrexate analogs)
RN 62828-70-0 HCAPLUS
CN Adenosine 5'-(trihydrogen diphosphate), 8-bromo-, 2'-(dihydrogen phosphate), P'.fwdarw.5'-ester with 3-(aminocarbonyl)-1-.beta.-D-ribofuranosylpyridinium inner salt (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



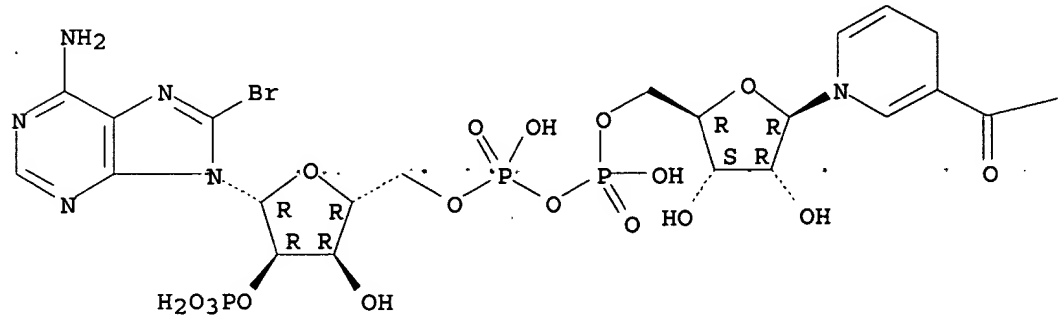
PAGE 1-B

—NH2

RN 246154-60-9 HCAPLUS
CN Adenosine 5'-(trihydrogen diphosphate), 8-bromo-, 2'-(dihydrogen phosphate), P'.fwdarw.5'-ester with 1,4-dihydro-1-.beta.-D-ribofuranosyl-3-pyridinecarboxamide (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



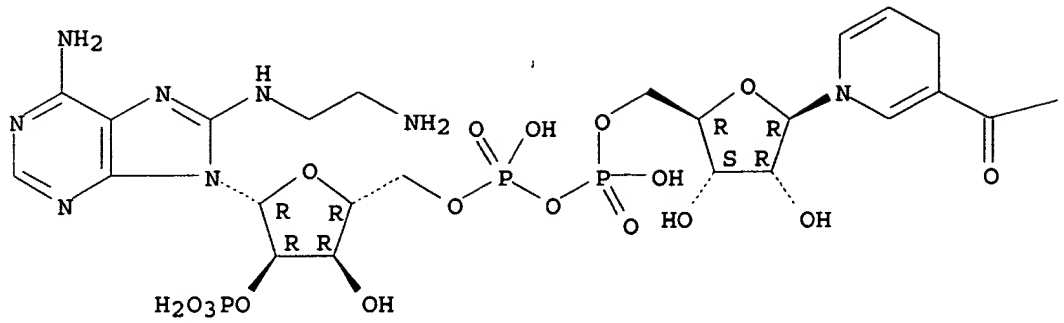
PAGE 1-B

—NH2

RN 246154-61-0 HCAPLUS
CN Adenosine 5'-(trihydrogen diphosphate), 8-[(2-aminoethyl)amino]-, 2'-(dihydrogen phosphate), P'.fwdarw.5'-ester with 1,4-dihydro-1-.beta.-D-ribofuranosyl-3-pyridinecarboxamide (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



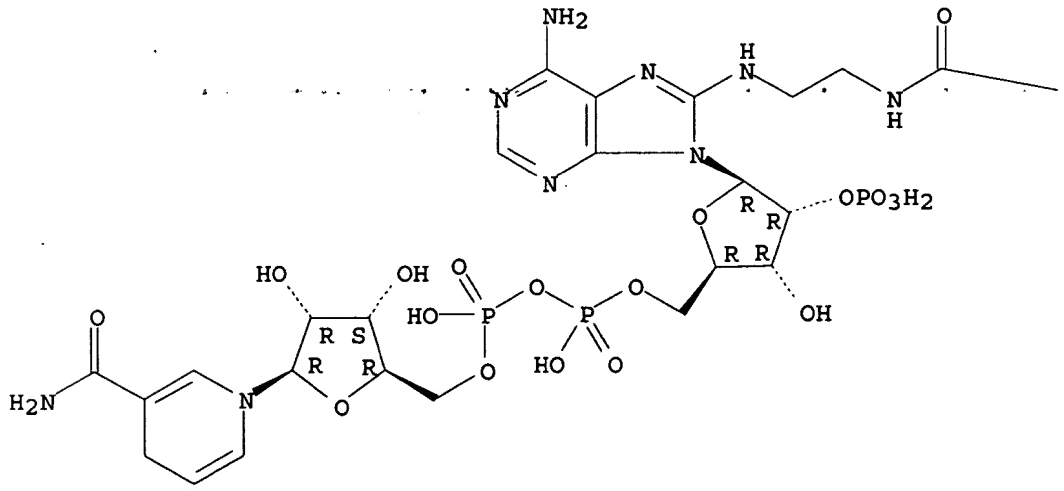
PAGE 1-B

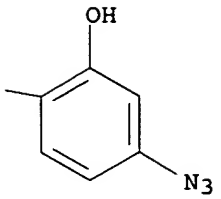
—NH2

RN 246154-62-1 HCAPLUS
CN Adenosine 5'-(trihydrogen diphosphate), 8-[[2-[(4-azido-2-hydroxybenzoyl)amino]ethyl]amino]-, 2'-(dihydrogen phosphate), P'.fwdarw.5'-ester with 1,4-dihydro-1-.beta.-D-ribofuranosyl-3-pyridinecarboxamide (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A





REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 6 OF 16 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:527193 HCAPLUS
DOCUMENT NUMBER: 129:166193
TITLE: Therapeutic treatment and prevention of infections with a bioactive material encapsulated within a biodegradable-biocompatible polymeric matrix
INVENTOR(S): Setterstrom, Jean A.; Van Hamont, John E.; Reid, Robert H.; Jacob, Elliot; Jeyanthi, Ramasubbu; Boedeker, Edgar C.; McQueen, Charles E.; Tice, Thomas R.; Roberts, F. Donald; Friden, Phil
PATENT ASSIGNEE(S): United States Dept. of the Army, USA; Van Hamont, John E.; et al.
SOURCE: PCT Int. Appl., 363 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 12
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9832427	A1	19980730	WO 1998-US1556	19980127
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 6309669	B1	20011030	US 1997-789734	19970127
AU 9863175	A1	19980818	AU 1998-63175	19980127

PRIORITY APPLN. INFO.:

US 1997-789734	A	19970127
US 1984-590308	B1	19840316
US 1992-867301	A2	19920410
US 1995-446148	A2	19950522
US 1995-446149	B2	19950522
US 1996-590973	B2	19960124
WO 1998-US1556	W	19980127

AB Novel burst-free, sustained release biocompatible and biodegradable microcapsules are disclosed which can be programmed to release their active core for variable durations ranging from 1-100 days in an aq. physiol. environment. The microcapsules are comprised of a core of polypeptide or other biol. active agent encapsulated in a matrix of poly(lactide/glycolide) copolymer, which may contain a pharmaceutically

acceptable adjuvant, as a blend of upcapped free carboxyl end group and end-capped forms ranging in ratios from 100/0 to 1/99.

IC ICM A61K009-52
ICS A61K047-30

CC 63-5 (Pharmaceuticals)
Section cross-reference(s): 1, 2, 15

IT **Immunoglobulins**
RL: BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(G, ampicillin-specific; prevention of infections with a bioactive material encapsulated within a biodegradable-biocompatible polymeric matrix)

IT AIDS (disease)
Acinetobacter
Actinomycetales
Adenoviridae
Adrenoceptor agonists
Aerococcus
Aeromonas
Allergy inhibitors
Alzheimer's disease
Analgesics
Anesthetics
Angiogenesis
Angiogenesis inhibitors
Anthelmintics
Anti-infective agents
Anti-inflammatory agents
Antiarrhythmics
Antiarthritics
Antibacterial agents
Antibiotics
Anticholesteremic agents
Anticoagulants
Anticoagulants
Anticonvulsants
Antidepressants
Antidiabetic agents
Antidiarrheals
Antiemetics
Antihistamines
Antihypertensives
Antimalarials
Antimigraine agents
Antiparkinsonian agents
Antipyretics
Antirheumatic agents
Antiserums
Antitumor agents
Antitussives
Antiulcer agents
Antiviral agents
Appetite depressants
Arbovirus
Arcanobacterium haemolyticum
Arenavirus
Asthma
Bacillus (bacterium genus)
Biocompatibility

Blood substitutes
Bordetella
Borrelia
Bronchodilators
Brucella
Cachexia
Calymmatobacterium
Campylobacter
Cardiopulmonary bypass
Cardiotonics
Cardiovascular agents
Cholinergic agonists
Clostridium
Contraceptives
Coronavirus
Corynebacterium
Cryptosporidium parvum
Cystic fibrosis
Cytomegalovirus
Cytotoxic agents
Decongestants
Diagnosis
Diarrhea
Dissolution rate
Diuretics
Drug bioavailability
Drug dependence
Ebola virus
Echinococcus
Electrolytes, biological
Emulsifying agents
Enterobacteriaceae
Enterococcus
Enterovirus
Epitopes
Erysipelothrix
Expectorants
Filovirus
Flavobacterium
Freeze drying
Fungicides
Gardnerella
Gram-negative bacteria
Gram-positive bacteria (Firmicutes)
Haemophilus
Haemophilus ducreyi
Helicobacter
Hepatitis A virus
Hepatitis B virus
Hepatitis C virus
Human herpesvirus 3
Human herpesvirus 4
Human **immunodeficiency** virus
Human **immunodeficiency** virus 1
Human parainfluenza virus
Human poliovirus
Hypercholesterolemia
Hypnotics and Sedatives
Immunization
Immunomodulators

Immunostimulants
Infection
Influenza virus
Kidney, disease
Lactococcus
Legionella
Leptospira
Leuconostoc
Listeria
Measles virus
Melanoma
Micrococcus
Molluscum contagiosum virus
Moraxella
Multiple sclerosis
Mumps virus
Muscle relaxants
Narcotics
Neisseria
Nervous system agents
Nutrients
Opioid antagonists
Osteoarthritis
Osteomyelitis
Osteoporosis
Ovary, neoplasm
Pancreas, neoplasm
Papillomavirus
Parasiticides
Parkinson's disease
Pediococcus
Planococcus (bacterium)
Plesiomonas
Pneumonia
Poxviridae
Pseudomonas
Psoriasis
Psychotropics
Rabies virus
Reoviridae
Respiratory syncytial virus
Rheumatoid arthritis
Rhinovirus
Rhodococcus
Rotavirus
Rothia (bacterium)
Rubella virus
Salmonella typhi
Sexually transmitted diseases
Shigella boydii
Shigella dysenteriae
Shigella flexneri
Shigella sonnei
Spirillum
Staphylococcus
Streptobacillus
Streptococcus
Thrombosis
Tranquilizers
Treponema

Vaccines
Vasodilators
Vibrio
Vibrio cholerae
Wolinella succinogenes
Yersinia
(prevention of infections with a bioactive material encapsulated within a biodegradable-biocompatible polymeric matrix)

IT 50-06-6, Phenobarbital, biological studies 50-12-4, Mephenytoin 50-18-0, Cyclophosphamide 50-23-7, Hydrocortisone 50-24-8, Prednisolone 50-28-2, 17.beta.-Estradiol, biological studies 50-33-9, Phenylbutazone, biological studies 50-52-2, Thioridazine 50-55-5, Reserpine 50-78-2, Aspirin 51-55-8, Atropine, biological studies 52-24-4, Thiotepa 52-76-6, Lynestrenol 53-03-2, Prednisone 53-16-7, Estrone, biological studies 53-86-1, Indomethacin 54-11-5, Nicotine 55-48-1, Atropine sulfate 55-63-0, Nitroglycerin 55-86-7, Nitrogen mustard 56-53-1, Diethyl stilbestrol 56-75-7, Chloramphenicol 57-27-2, Morphine, biological studies 57-33-0, Sodium pentobarbital 57-42-1, Meperidine 57-53-4, Meprobamate 57-63-6, Ethinyl estradiol 57-85-2, Testosterone propionate 57-92-1, Streptomycin a, biological studies 58-08-2, Caffeine, biological studies 58-14-0, Pyrimethamine 58-22-0 58-25-3, Chlordiazepoxide 58-39-9, Perphenazine 58-73-1, Diphenhydramine 59-01-8, Kanamycin a 59-05-2, Methotrexate 59-92-7, L-Dopa, biological studies 61-33-6, Penicillin g, biological studies 67-20-9, Nitrofurantoin 68-22-4, Norethisterone 68-23-5, Norethynodrel 69-09-0, Chlorpromazine hydrochloride 69-53-4, Ampicillin 69-72-7D, Salicylic acid, derivs. 71-58-9, Medroxyprogesterone acetate 72-33-3, Mestranol 76-57-3, Codeine 79-57-2, Oxytetracycline 79-64-1, Dimethisterone 91-81-6, Tripelennamine 103-90-2, Acetaminophen 113-15-5, Ergotamine 114-07-8, Erythromycin 114-49-8, Hyoscine hydrobromide 121-54-0 122-09-8, Phentermine 125-29-1, Dihydrocodeinone 125-71-3, Dextromethorphan 127-48-0, Trimethadione 128-62-1, Noscapine 145-94-8, Chlorindanol 148-82-3, Melphalan 155-41-9, Methscopolamine bromide 288-32-4D, Imidazole, derivs. 297-76-7, Ethynodiol diacetate 302-22-7, Chlormadinone acetate 305-03-3, Chlorambucil 309-43-3, Sodium secobarbital 315-30-0, Allopurinol 434-03-7, Ethisterone 439-14-5, Diazepam 443-48-1, Metronidazole 469-62-5 471-34-1, Calcium carbonate, biological studies 497-19-8, Sodium carbonate, biological studies **523-87-5**, Dimenhydrinate 546-93-0, Magnesium carbonate 578-66-5D, 8-Aminoquinoline, derivs. 578-68-7D, 4-Aminoquinoline, derivs. 595-33-5, Megestrol acetate 738-70-5, Trimethoprim 846-50-4, Temazepam 1397-89-3, Amphotericin b 1397-94-0, Antimycin a 1403-66-3, Gentamicin 1404-26-8, Polymyxin b 1404-90-6, Vancomycin 4696-76-8, Kanamycin b 5588-33-0, Mesoridazine 5633-18-1, Melengestrol 5786-21-0, Clozapine 5800-19-1, Metiapine 6533-00-2, Norgestrel 7447-40-7, Potassium chloride (KCl), biological studies 8063-07-8, Kanamycin 9000-83-3, Atpase 9000-92-4, Amylase 9001-62-1, Lipase 9001-63-2, Muramidase 9001-67-6, Neuraminidase 9001-78-9, Alkaline phosphatase 9001-99-4, Ribonuclease 9002-02-2, Succinic acid dehydrogenase 9002-07-7, Trypsin 9004-07-3, Chymotrypsin 9004-10-8, Insulin, biological studies 9025-82-5, Phosphodiesterase 9029-12-3, Glutamic acid dehydrogenase 9035-74-9, Glycogen phosphorylase 9046-27-9, .gamma.-Glutamyltranspeptidase 9079-67-8 10118-90-8, Minocycline 11111-12-9, Cephalosporins 13292-46-1, Rifampin 14271-04-6 21645-51-2, Aluminum hydroxide, biological studies 22232-71-9, Mazindol 24730-10-7, Dihydroergocristine methanesulfonate 25447-66-9 26780-50-7, Poly(lactide co-glycolide) 26787-78-0, Amoxicillin 30516-87-1, Azt 32986-56-4, Tobramycin 35189-28-7, Norgestimate 37205-61-1, Proteinase inhibitor 37517-28-5, Amikacin 53678-77-6D, Muramyl dipeptide, derivs.

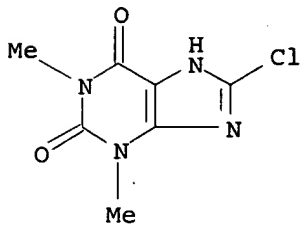
53994-73-3, Cefaclor 55268-75-2, Cefuroxime 61036-62-2, Teicoplanin
64221-86-9, Imipenem 80738-43-8, Lincosamide 81103-11-9,
Clarithromycin 82419-36-1, Ofloxacin 85721-33-1, Ciprofloxacin
RL: BPR (Biological process); BSU (Biological study, unclassified); DEV
(Device component use); PEP (Physical, engineering or chemical process);
THU (Therapeutic use); BIOL (Biological study); PROC (Process);
USES (Uses)
(prevention of infections with a bioactive material encapsulated within
a biodegradable-biocompatible polymeric matrix)

IT **523-87-5**, Dimenhydrinate
RL: BPR (Biological process); BSU (Biological study, unclassified); DEV
(Device component use); PEP (Physical, engineering or chemical process);
THU (Therapeutic use); BIOL (Biological study); PROC (Process);
USES (Uses)
(prevention of infections with a bioactive material encapsulated within
a biodegradable-biocompatible polymeric matrix)

RN 523-87-5 HCAPLUS
CN 1H-Purine-2,6-dione, 8-chloro-3,7-dihydro-1,3-dimethyl-, compd. with
2-(diphenylmethoxy)-N,N-dimethylethanamine (1:1) (9CI) (CA INDEX NAME)

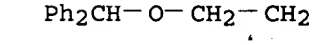
CM 1

CRN 85-18-7
CMF C7 H7 Cl N4 O2



CM 2

CRN 58-73-1
CMF C17 H21 N O



REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 7 OF 16 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:467612 HCAPLUS
DOCUMENT NUMBER: 129:270220
TITLE: Leishmania amazonensis infection is reduced in macrophages treated with guanine ribonucleosides
AUTHOR(S): Giorgio, Selma; Barao, Sandra C.; Augusto, Ohara; Kwee, Jolie K.
CORPORATE SOURCE: Instituto de Biologia, Departamento de Parasitologia, Universidade Estadual de Campinas, Sao Paulo, 13083-970, Brazil
SOURCE: Acta Tropica (1998), 70(1), 119-122

CODEN: ACTRAQ; ISSN: 0001-706X
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The effect of several guanine ribonucleosides on the cytotoxicity of macrophages against the parasite Leishmania amazonensis.

CC 1-7 (Pharmacology)

ST Leishmania amazonensis infection macrophage guanine ribonucleoside; **immunostimulant** guanine ribonucleoside macrophage cytotoxicity Leishmania

IT **Immunostimulants**
Leishmania amazonensis
Macrophage
(Leishmania amazonensis infection is reduced in macrophages treated with guanine ribonucleosides)

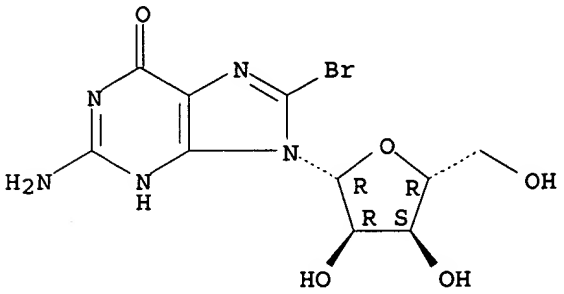
IT 3868-31-3 **4016-63-1**, 8-Bromoguanosine 26001-38-7, 8-Mercaptoguanosine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(Leishmania amazonensis infection is reduced in macrophages treated with guanine ribonucleosides)

IT **4016-63-1**, 8-Bromoguanosine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(Leishmania amazonensis infection is reduced in macrophages treated with guanine ribonucleosides)

RN 4016-63-1 HCAPLUS

CN Guanosine, 8-bromo- (7CI, 8CI, 9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L9 ANSWER 8 OF 16 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1998:293319 HCAPLUS
DOCUMENT NUMBER: 129:579

TITLE: Induction of viral mutation by incorporation of miscoding ribonucleoside analogs into viral RNA

INVENTOR(S): Loeb, Lawrence A.; Mullins, James I.
PATENT ASSIGNEE(S): University of Washington, USA; Loeb, Lawrence A.; Mullins, James I.

SOURCE: PCT Int. Appl., 60 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9818324	A1	19980507	WO 1997-US19670	19971027
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9850959	A1	19980522	AU 1998-50959	19971027
AU 740916	B2	20011115		
EP 948256	A1	19991013	EP 1997-913882	19971027
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
US 6063628	A	20000516	US 1997-958065	19971027
JP 2001525797	T2	20011211	JP 1998-520739	19971027

PRIORITY APPLN. INFO.:	US 1996-29404P	P	19961028
	US 1997-40535P	P	19970227
	WO 1997-US19670	W	19971027

AB The invention is directed to the identification and use of ribonucleoside analogs to induce the mutation of an RNA virus, including HIV and HCV, or a virus which otherwise replicates through an RNA intermediate. The increase in the mutation rate of the virus results in reduced viability of progeny generations of the virus, thereby inhibiting viral replication. In addn. to these methods and related compns., the invention provides methods and combinatorial chem. libraries for screening ribonucleoside analogs for mutagenic potential.

IC ICM A01N043-04
ICS A61K031-70; C12N007-04; C12N007-06; C12Q001-68; C12Q001-70

CC 1-5 (Pharmacology)
Section cross-reference(s): 63

IT Animal tissue culture
Anti-AIDS agents
Antiviral agents
Combinatorial library
Coronavirus
Dengue virus
Drug delivery systems
Drug screening
Feline **immunodeficiency** virus
Feline leukemia virus
Hepatitis A virus
Hepatitis B virus
Hepatitis C virus
Human T-lymphotropic virus 1
Human T-lymphotropic virus 2
Human **immunodeficiency** virus
Human **immunodeficiency** virus 1
Human **immunodeficiency** virus 2
Influenza virus
Mutation
RNA viruses
Respiratory syncytial virus
Retroviridae
Simian **immunodeficiency** virus
Vesicular stomatitis virus

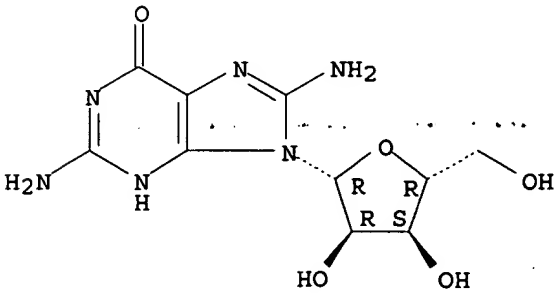
(induction of viral mutation by incorporation of miscoding ribonucleoside analogs into viral RNA, and screening method)

IT 58-61-7D, Adenosine, derivs., biological studies 58-96-8D, Uridine, derivs. 65-46-3D, Cytidine, derivs. 118-00-3D, Guanosine, derivs., biological studies 957-77-7, 5-Hydroxyuridine 957-77-7D, 5-Hydroxyuridine, derivs. 1867-73-8 1867-73-8D, derivs. 2140-64-9, 3-Methylcytidine 2140-64-9D, 3-Methylcytidine, derivs. 2140-69-4, 3-Methyluridine 2140-69-4D, 3-Methyluridine, derivs. 2149-76-0, 5-Aminouridine 2149-76-0D, 5-Aminouridine, derivs. 3066-86-2, 5-Bromocytidine 3066-86-2D, 5-Bromocytidine, derivs. 3868-31-3, 8-Hydroxyguanosine 3868-31-3D, 8-Hydroxyguanosine, derivs. **3868-32-4**, 8-Aminoguanosine **3868-32-4D**, 8-Aminoguanosine, derivs. 7803-88-5 7803-88-5D, derivs. 13007-43-7 13007-43-7D, derivs. 23899-77-6, 5-Aminocytidine 23899-77-6D, 5-Aminocytidine, derivs. 25130-29-4, 5-Chlorocytidine 25130-29-4D, 5-Chlorocytidine, derivs. 33962-59-3 33962-59-3D, derivs. 34218-77-4 34218-77-4D, derivs. 39007-51-7 39007-51-7D, derivs. 39007-52-8 39007-52-8D, derivs. 39638-73-8 39638-73-8D, derivs. 39708-01-5 39708-01-5D, derivs. 53337-88-5 53337-88-5D, derivs. 53337-89-6 53337-89-6D, derivs. 57294-74-3 57294-74-3D, derivs. 59495-20-4 59495-20-4D, derivs. 72055-62-0, 3-Methyladenosine 72055-62-0D, 3-Methyladenosine, derivs. 82773-20-4 82773-20-4D, derivs. 100997-68-0 100997-68-0D, derivs. 108060-85-1 108060-85-1D, derivs. 137248-64-7 137248-64-7D, derivs. 207340-54-3 207340-54-3D, derivs. 207340-56-5 207340-56-5D, derivs. 207340-58-7 207340-58-7D, derivs.
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(induction of viral mutation by incorporation of miscoding ribonucleoside analogs into viral RNA, and screening method)

IT **3868-32-4**, 8-Aminoguanosine **3868-32-4D**, 8-Aminoguanosine, derivs.
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(induction of viral mutation by incorporation of miscoding ribonucleoside analogs into viral RNA, and screening method)

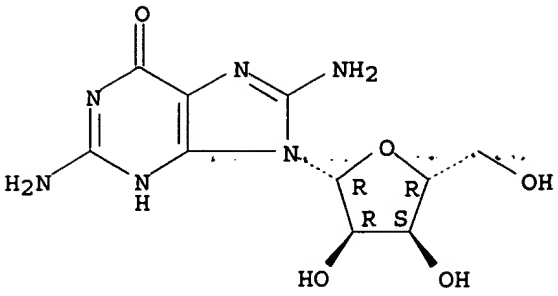
RN 3868-32-4 HCAPLUS
CN Guanosine, 8-amino- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



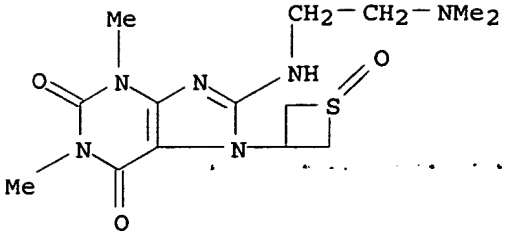
RN 3868-32-4 HCAPLUS
CN Guanosine, 8-amino- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

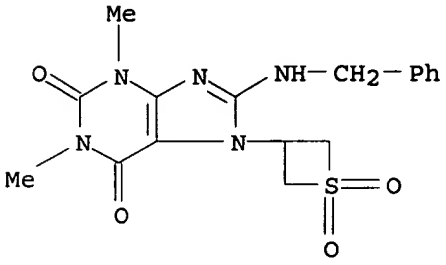


REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 9 OF 16 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:260235 HCAPLUS
DOCUMENT NUMBER: 129:49337
TITLE: Synthesis of biologically active derivatives of xanthine and benzimidazole
AUTHOR(S): Khaliullin, F. A.; Kataev, V. A.; Alekhin, E. K.; Volkova, S. S.; Nasyrov, Kh. M.; Strokin, Yu. V.
CORPORATE SOURCE: Bashk. Gos. Med. Univ., Ufa, Russia
SOURCE: Bashkirskii Khimicheskii Zhurnal (1997), 4(4), 59-62
CODEN: BKZHFU; ISSN: 0869-8406
PUBLISHER: Izdatel'stvo "Reaktiv".
DOCUMENT TYPE: Journal
LANGUAGE: Russian
AB A study was done of reactions of amines with products of xanthines or benzimidazoles alkylation by epithiochlorohydrin. 2-Amino-substituted 1-(3-thietanyl)benzimidazoles were synthesized from 1-(3-thietanyl)-2-chlorobenzimidazole. 8-Amino-substituted derivs. were formed from 8-bromo-1,3-dimethyl-7-(1-oxothietanyl-3)- and 8-bromo-1,3-dimethyl-7-(1,1-dioxothietanyl-3)xanthines. 2-Amino-substituted 2,3-dihydrothiazolo[3.2-a]benzimidazoles were synthesized from 2-methylsulfonyl-1-(2,3-epithiopropyl)benzimidazole. Immunotropic and anti-inflammatory activities of the synthesized compds. were discovered.
CC 1-7 (Pharmacology)
Section cross-reference(s): 28
IT Anti-inflammatory agents
Immunomodulators
(prepn. of biol. active derivs. of xanthine and benzimidazole)
IT 51-17-2DP, Benzimidazole, derivs. 69-89-6DP, Xanthine, derivs.
182193-10-8P 208577-04-2P 208577-05-3P 208577-06-4P 208577-07-5P
208577-08-6P 208577-09-7P **208577-10-0P** 208577-11-1P
208577-12-2P 208577-13-3P 208577-14-4P 208577-15-5P 208577-16-6P
208577-17-7P
RL: SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of biol. active derivs. of xanthine and benzimidazole)
IT **208577-08-6P 208577-10-0P**
RL: SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of biol. active derivs. of xanthine and benzimidazole)
RN 208577-08-6 HCAPLUS
CN 1H-Purine-2,6-dione, 8-[[2-(dimethylamino)ethyl]amino]-3,7-dihydro-1,3-dimethyl-7-(1-oxido-3-thietanyl)- (9CI) (CA INDEX NAME)



RN 208577-10-0 HCAPLUS
CN 1H-Purine-2,6-dione, 7-(1,1-dioxido-3-thietanyl)-3,7-dihydro-1,3-dimethyl-8-[(phenylmethyl)amino]- (9CI) (CA INDEX NAME)



L9 ANSWER 10 OF 16 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:797999 HCAPLUS
DOCUMENT NUMBER: 128:102345
TITLE: Preparation of 3-O-(.alpha.-D-glucopyranosyl)ribofuranose and 3'-O-(.alpha.-D-glucopyranosyl)-purine nucleoside polyphosphate derivatives having affinity to inositol 1,4,5-triphosphate (InsP3) receptor
INVENTOR(S): Hotoda, Hitoshi; Murayama, Kazuhiro; Kanako, Masakatsu; Takahashi, Masaaki; Tanzawa, Kazuhiko; Takahashi, Shuji
PATENT ASSIGNEE(S): Sankyo Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 33 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 09316093	A2	19971209	JP 1997-65684	19970319

PRIORITY APPLN. INFO.: JP 1996-73664 19960328
OTHER SOURCE(S): MARPAT 128:102345
AB The title compds. [I; R1 - R6 = H, P(O)(OH)2; R7 = H, C1-4 alkoxy, Q, Q1; wherein Y = OH, NH2; X = H, halo], which increase cellular calcium ion concn., are prepd. They are useful for the treatment of brain diseases such as senile dementia, Alzheimer's disease, and Huntington's disease and as antihypertensives and immunostimulants activating immune cells and for the treatment of bedsore, upper skin ulcers, and type-I diabetes by enhancing insulin secretion (no data). Thus, 80 mg adenophostin A was

dissolved in a 1M AcONa buffer (pH 4), followed by adding 10 mg Br, and the resulting mixt. was stirred at room temp. for 5 days to give 8-bromoadenophostin A (II). Pharmaceutical formulations such as hard capsule, soft capsule, tablet, injection, and suspension formulations contg. II were prepd.

IC ICM C07H019-20
ICS A61K031-70; C07H019-167

CC 33-9 (Carbohydrates)
Section cross-reference(s): 1, 63

ST glucopyranosylribofuranose polyphosphate prepn; inositol triphosphate receptor affinity; glucopyranosyl purine nucleoside polyphosphate prepn; senile dementia treatment glucopyranosylpurine nucleoside polyphosphate; Alzheimer disease treatment glucopyranosylpurine nucleoside polyphosphate; Huntington disease treatment glucopyranosylpurine nucleoside polyphosphate; antihypertensive treatment glucopyranosylpurine nucleoside polyphosphate; **immunostimulant** treatment glucopyranosylpurine nucleoside polyphosphate; bedsore treatment glucopyranosylpurine nucleoside polyphosphate; skin ulcer treatment glucopyranosylpurine nucleoside polyphosphate; type I diabetes insulin secretion enhancement

IT Alzheimer's disease
Antihypertensives
Antiulcer agents
Immunostimulants
(prepn. of O-(.alpha.-D-glucopyranosyl)ribofuranose and O-(.alpha.-D-glucopyranosyl)-purine nucleoside polyphosphate derivs. having affinity to inositol triphosphate receptor for disease treatment)

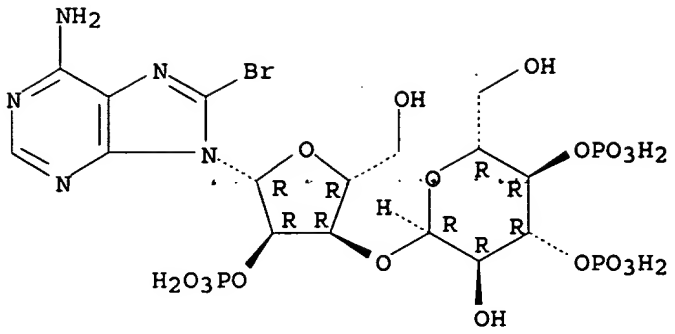
IT **200284-11-3P 200284-13-5P** 200284-14-6P 200284-16-8P 200284-18-0P 200284-20-4P 200284-22-6P 200284-24-8P 200284-26-0P 200284-27-1P
RL: SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of O-(.alpha.-D-glucopyranosyl)ribofuranose and O-(.alpha.-D-glucopyranosyl)-purine nucleoside polyphosphate derivs. having affinity to inositol triphosphate receptor for disease treatment)

IT **200284-11-3P 200284-13-5P**
RL: SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of O-(.alpha.-D-glucopyranosyl)ribofuranose and O-(.alpha.-D-glucopyranosyl)-purine nucleoside polyphosphate derivs. having affinity to inositol triphosphate receptor for disease treatment)

RN 200284-11-3 HCAPLUS

CN 2'-Adenylic acid, 8-bromo-3'-O-(3,4-di-O-phosphono-.alpha.-D-glucopyranosyl)-, sodium salt (9CI) (CA INDEX NAME)

Absolute stereochemistry.



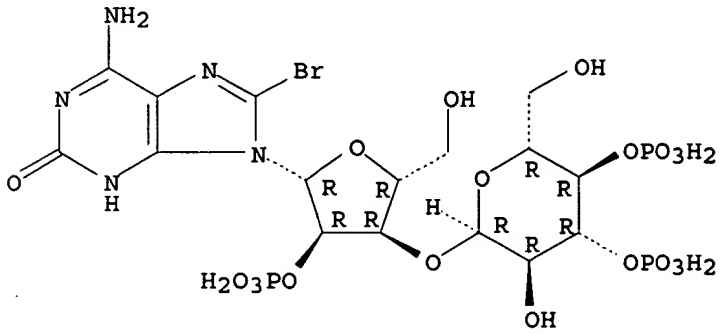
●x Na

RN 200284-13-5 HCAPLUS
CN 2'-Adenylic acid, 8-bromo-3'-O-(3,4-di-O-phosphono-.alpha.-D-glucopyranosyl)-1,2-dihydro-2-oxo-, compd. with N,N-diethylethanamine (9CI) (CA INDEX NAME)

CM 1

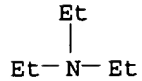
CRN 200284-12-4
CMF C16 H25 Br N5 O19 P3

Absolute stereochemistry.



CM 2

CRN 121-44-8
CMF C6 H15 N



L9 ANSWER 11 OF 16 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:344515 HCAPLUS

DOCUMENT NUMBER: 126:317285
TITLE: Purine and guanine derivatives as PNP inhibitors
INVENTOR(S): Beasley, Steven Colin; Montana, John Gary
PATENT ASSIGNEE(S): Chiroscience Limited, UK; Beasley, Steven Colin; Montana, John Gary
SOURCE: PCT Int. Appl., 37 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9712887	A1	19970410	WO 1996-GB2444	19961007
W: AL, AM, AU, AZ, BB, BG, BR, BY, CA, CN, CZ, EE, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2226958	AA	19970410	CA 1996-2226958	19961007
AU 9671402	A1	19970428	AU 1996-71402	19961007
ZA 9608439	A	19971121	ZA 1996-8439	19961007
EP 873339	A1	19981028	EP 1996-932726	19961007
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
JP 11512734	T2	19991102	JP 1996-514082	19961007
US 5912252	A	19990615	US 1997-849438	19970519

PRIORITY APPLN. INFO.: GB 1995-20364 A 19951005
WO 1996-GB2444 W 19961007
OTHER SOURCE(S): MARPAT 126:317285

AB Purines I [n = 1, 2; R1 = H, NH2, halogen; R2 = H, NH2; R3 = alkyl, haloalkyl; R4, R5 = H, CO2H, alkoxycarbonyl, NHSO2CF3, tetrazole, (un)substituted alkyl] were prepd. for use as purine nucleoside phosphorylase inhibitors and immunosuppressants (no data). Thus, Me3CCH2CH2OH was converted to its mesylate and treated with 2,8-diamino-6-benzyloxypurine to give 2,8-diamino-6-benzyloxy-9-(3,3-dimethylbutyl)purine. This compd. was hydrolyzed to 8-amino-9-(3,3-dimethylbutyl)guanine HCl.

IC ICM C07D473-00
ICS C07D473-18; C07D473-30; A61K031-52

CC 26-9 (Biomolecules and Their Synthetic Analogs)
Section cross-reference(s): 1

ST aminoalkylguanine prepn **immunosuppressant**; guanine alkylamino prepn **immunosuppressant**; purine nucleoside phosphorylase inhibitor aminoalkylguanine prepn

IT **Immunosuppressants**
(prepn. of 8-amino-9-alkylguanines as purine nucleoside phosphorylase inhibitors)

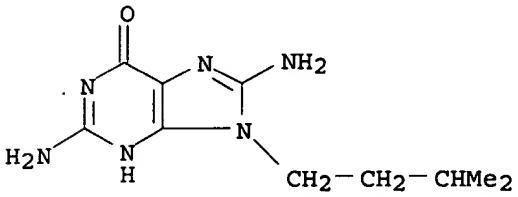
IT **189371-90-2P**
RL: RCT (Reactant); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(prepn. of 8-amino-9-alkylguanines as purine nucleoside phosphorylase inhibitors)

IT **189371-88-8P 189371-89-9P 189371-91-3P 189371-92-4P 189371-93-5P**
RL: SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)

(prepn. of 8-amino-9-alkylguanines as purine nucleoside phosphorylase inhibitors)

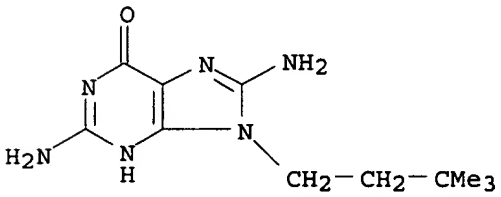
IT **189371-90-2P**
RL: RCT (Reactant); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(prepn. of 8-amino-9-alkylguanines as purine nucleoside phosphorylase inhibitors)

RN 189371-90-2 HCAPLUS
CN 6H-Purin-6-one, 2,8-diamino-1,9-dihydro-9-(3-methylbutyl)- (9CI) (CA INDEX NAME)



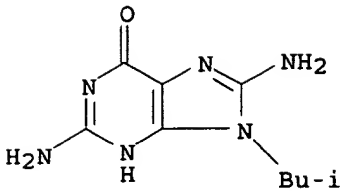
IT **189371-88-8P 189371-89-9P 189371-91-3P**
189371-92-4P 189371-93-5P
RL: SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of 8-amino-9-alkylguanines as purine nucleoside phosphorylase inhibitors)

RN 189371-88-8 HCAPLUS
CN 6H-Purin-6-one, 2,8-diamino-9-(3,3-dimethylbutyl)-1,9-dihydro-, dihydrochloride (9CI) (CA INDEX NAME)



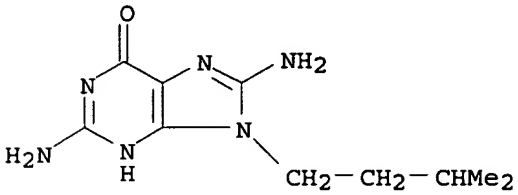
●2 HCl

RN 189371-89-9 HCAPLUS
CN 6H-Purin-6-one, 2,8-diamino-1,9-dihydro-9-(2-methylpropyl)-, dihydrochloride (9CI) (CA INDEX NAME)



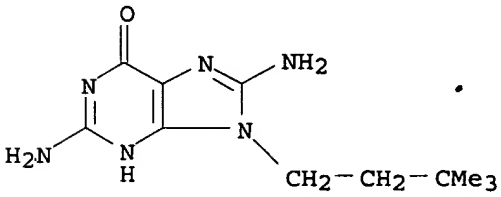
● 2 HCl

RN 189371-91-3 HCAPLUS
CN 6H-Purin-6-one, 2,8-diamino-1,9-dihydro-9-(3-methylbutyl)-, dihydrochloride (9CI) (CA INDEX NAME)

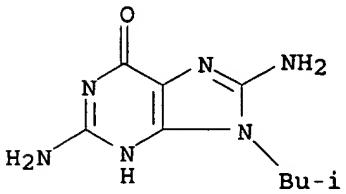


● 2 HCl

RN 189371-92-4 HCAPLUS
CN 6H-Purin-6-one, 2,8-diamino-9-(3,3-dimethylbutyl)-1,9-dihydro- (9CI) (CA INDEX NAME)



RN 189371-93-5 HCAPLUS
CN 6H-Purin-6-one, 2,8-diamino-1,9-dihydro-9-(2-methylpropyl)- (9CI) (CA INDEX NAME)



L9 ANSWER 12 OF 16 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1996:153514 HCAPLUS
DOCUMENT NUMBER: 124:194287
TITLE: Methods of screening for nucleoside analogs that are incorporated by HIV reverse transcriptase and cause incorrect base pairing
INVENTOR(S): Loeb, Lawrence A.; Essigmann, John M.
PATENT ASSIGNEE(S): Darwin Molecular Corp., USA
SOURCE: PCT Int. Appl., 33 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9600797	A1	19960111	WO 1995-US7937	19950622
W: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IS, JP, KG, KP, KR, KZ, LK, LR, LT, LV, MD, MG, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TT, UA, UZ, VN				
RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5512431	A	19960430	US 1994-268686	19940629
CA 2194153	AA	19960111	CA 1995-2194153	19950622
AU 9529475	A1	19960125	AU 1995-29475	19950622
AU 706223	B2	19990610		
EP 767842	A1	19970416	EP 1995-925292	19950622
EP 767842	B1	20000927		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
JP 10508183	T2	19980818	JP 1995-503320	19950622
EP 1004675	A2	20000531	EP 2000-101250	19950622
EP 1004675	A3	20000920		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE				
AT 196658	E	20001015	AT 1995-925292	19950622
US 6132776	A	20001017	US 1997-876715	19970616

PRIORITY APPLN. INFO.:
US 1994-268686 A 19940629
EP 1995-925292 A3 19950622
WO 1995-US7937 W 19950622
US 1996-641094 B1 19960429

AB Methods and compns. related to HIV are disclosed. Using the methods of the invention, nucleoside analogs may be screened for the ability to be incorporated by reverse transcriptase of human immunodeficiency virus (HIV RT) and cause incorrect base pairing. Progressive mutation of the virus by such nucleoside analogs renders it non-viable. The nucleoside analogs are useful for the manuf. of a medicament for treatment of HIV infection.

IC ICM C12Q001-68
ICS C12Q001-70; C07H019-073; A61K031-70

CC 1-1 (Pharmacology)
Section cross-reference(s): 7

IT Virus, animal
(human **immunodeficiency**, screening for nucleoside analogs incorporated by HIV reverse transcriptase and cause incorrect base pairing)

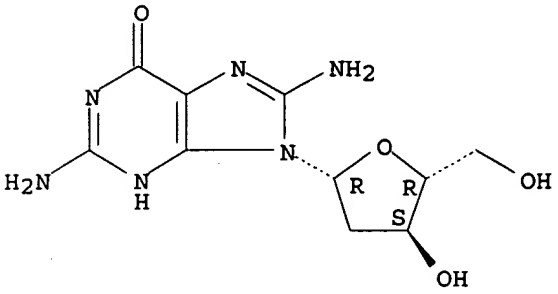
IT 964-21-6 7226-77-9, 5-Hydroxymethyldeoxycytidine **13389-04-3**, 8-Aminodeoxyguanosine 50591-13-4 50704-46-6 52278-77-0 59495-22-6 68498-25-9 68498-26-0 85754-75-2 87539-54-6 88847-89-6

121055-53-6 174305-68-1 174305-69-2 174305-70-5
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(screening for nucleoside analogs incorporated by HIV reverse transcriptase and cause incorrect base pairing)

IT **13389-04-3**, 8-Aminodeoxyguanosine
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(screening for nucleoside analogs incorporated by HIV reverse transcriptase and cause incorrect base pairing)

RN 13389-04-3 HCAPLUS
CN Guanosine, 8-amino-2'-deoxy- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L9 ANSWER 13 OF 16 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1995:594357 HCAPLUS
DOCUMENT NUMBER: 123:2743
TITLE: Systematic evolution of ligands by exponential enrichment using photoselection of nucleic acid ligands and using the exponential selection and enrichment method SELEX in solution
INVENTOR(S): Gold, Larry; Willis, Michael; Koch, Tad; Ringquist, Steven; Jensen, Kirk; Atkinson, Brent
PATENT ASSIGNEE(S): University Research Corp., USA
SOURCE: PCT Int. Appl., 136 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 118
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9508003	A1	19950323	WO 1994-US10562	19940916
W: AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, LV, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, US, US, UZ, VN				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2169535	AA	19950323	CA 1994-2169535	19940916
AU 9477987	A1	19950403	AU 1994-77987	19940916
AU 692185	B2	19980604		
EP 736105	A1	19961009	EP 1994-928621	19940916
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
JP 09502616	T2	19970318	JP 1994-509401	19940916
US 5763177	A	19980609	US 1996-612895	19960308
AU 9852711	A1	19980521	AU 1998-52711	19980123

AU 728910 B2 20000118
US 2002106652 A1 20020808 US 2001-882246 20010614
PRIORITY APPLN. INFO.: US 1993-123935 A 19930917
US 1993-143564 A 19931025
US 1990-536428 B2 19900611
US 1991-714131 A2 19910610
US 1992-931473 A2 19920817
WO 1994-US10562 W 19940916
US 1996-612895 A1 19960308
US 1998-93293 A3 19980608
US 1999-459553 A3 19991213

AB A method for identifying nucleic acid ligands for target mols. using the SELEX procedure in which the candidate nucleic acids contain photoreactive groups is described. The complexes of increased affinity nucleic acids and target mols. formed in the procedure are crosslinked by irradn. to facilitate sepn. from unbound nucleic acids. In other methods partitioning of high and low affinity nucleic acids is facilitated by primer extension steps as shown in the figure in which chain termination nucleotides, digestion resistant nucleotides or nucleotides that allow retention of the cDNA product on an affinity matrix are differentially incorporated into the cDNA products of either the high or low affinity nucleic acids and the cDNA products are treated accordingly to amplification, enzymic or chem. digestion or by contact with an affinity matrix. The oligonucleotides may be prepd. chem. or enzymically by incorporation of reactive dNTP's into a polymerase reaction. The method is demonstrated by selecting oligonucleotides that bind to the R17 coat protein.

IC ICM C12Q001-68
ICS C07H021-04; C07H021-02
CC 3-1 (Biochemical Genetics)
Section cross-reference(s): 9, 63

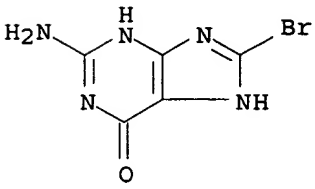
IT Virus, animal
(human **immunodeficiency** 1, photoreactive ligand-specific oligonucleotides against rev gene of, selection of; systematic evolution of ligands by exponential enrichment in soln. using photoselection of nucleic acid ligands)

IT 51-20-7D, 5-Bromouracil, oligonucleotides contg. 54-42-2D, oligonucleotides contg. 59-14-3D, oligonucleotides contg. 591-28-6D, 4-Thiouracil, oligonucleotides contg. 611-53-0D, oligonucleotides contg. 696-07-1D, 5-Iodouracil, oligonucleotides contg. 1122-44-7D, 5-Iodocytosine, oligonucleotides contg. 2240-25-7D, 5-Bromocytosine, oligonucleotides contg. **3066-84-0D**, 8-Bromoguanine, oligonucleotides contg. **6974-78-3D**, 8-Bromoadenine, oligonucleotides contg. **10357-68-3D**, 8-Bromoxanthine, oligonucleotides contg. **14985-44-5D**, oligonucleotides contg. **19690-18-7D**, oligonucleotides contg. **19690-20-1D**, oligonucleotides contg. **19690-21-2D**, oligonucleotides contg. 22276-99-9D, oligonucleotides contg. 34617-95-3D, oligonucleotides contg. **56046-36-7D**, 8-Bromohypoxanthine, oligonucleotides contg. 62785-92-6D, oligonucleotides contg. **64761-27-9D**, oligonucleotides contg. 79270-98-7D, 8-Azidoadenine, oligonucleotides contg. 163622-41-1D, oligonucleotides contg. 163622-42-2D, oligonucleotides contg. 163622-43-3D, oligonucleotides contg. 163622-44-4D, oligonucleotides contg. 163622-45-5D, oligonucleotides contg. 163622-46-6D, oligonucleotides contg. 163622-47-7D, oligonucleotides contg. 163622-48-8D, oligonucleotides contg. 163622-49-9D, oligonucleotides contg. 163622-50-2D, oligonucleotides contg. 163622-51-3D, oligonucleotides contg. 163622-52-4D, oligonucleotides contg.
RL: ARU (Analytical role, unclassified); BUU (Biological use,

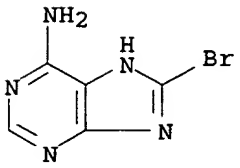
unclassified); NUU (Other use, unclassified); **THU (Therapeutic use)**; ANST (Analytical study); BIOL (Biological study); USES (Uses)
(as photoreactive group; systematic evolution of ligands by exponential enrichment in soln. using photoselection of nucleic acid ligands)

IT **3066-84-0D**, 8-Bromoguanine, oligonucleotides contg.
6974-78-3D, 8-Bromoadenine, oligonucleotides contg.
10357-68-3D, 8-Bromoxanthine, oligonucleotides contg.
14985-44-5D, oligonucleotides contg. **19690-18-7D**, oligonucleotides contg. **19690-20-1D**, oligonucleotides contg. **19690-21-2D**, oligonucleotides contg. **56046-36-7D**, 8-Bromohypoxanthine, oligonucleotides contg. **64761-27-9D**, oligonucleotides contg.
RL: ARU (Analytical role, unclassified); BUU (Biological use, unclassified); NUU (Other use, unclassified); **THU (Therapeutic use)**; ANST (Analytical study); BIOL (Biological study); USES (Uses)
(as photoreactive group; systematic evolution of ligands by exponential enrichment in soln. using photoselection of nucleic acid ligands)

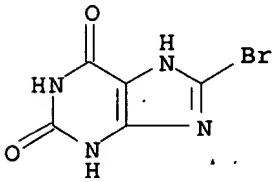
RN 3066-84-0 HCAPLUS
CN 6H-Purin-6-one, 2-amino-8-bromo-1,7-dihydro- (9CI) (CA INDEX NAME)



RN 6974-78-3 HCAPLUS
CN 1H-Purin-6-amine, 8-bromo- (9CI) (CA INDEX NAME)

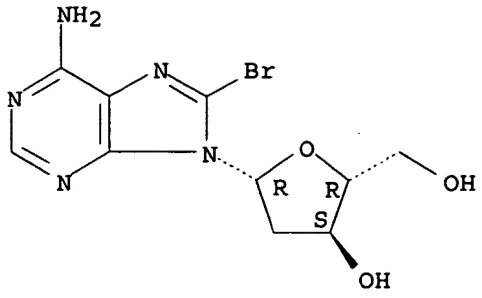


RN 10357-68-3 HCAPLUS
CN 1H-Purine-2,6-dione, 8-bromo-3,7-dihydro- (9CI) (CA INDEX NAME)

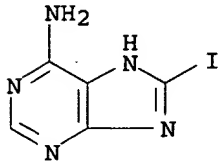


RN 14985-44-5 HCAPLUS
CN Adenosine, 8-bromo-2'-deoxy- (7CI, 8CI, 9CI) (CA INDEX NAME)

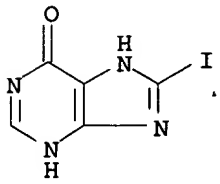
Absolute stereochemistry.



RN 19690-18-7 HCAPLUS
CN 1H-Purin-6-amine, 8-iodo- (9CI) (CA INDEX NAME)



RN 19690-20-1 HCAPLUS
CN 6H-Purin-6-one, 1,7-dihydro-8-iodo- (9CI) (CA INDEX NAME)



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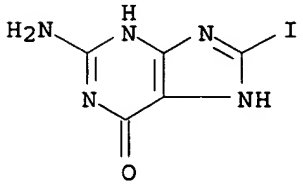
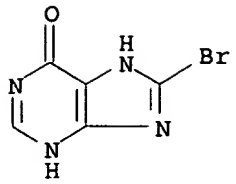
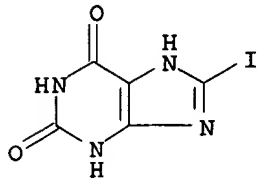
CN 6H-Purin-6-one, 2-amino-1,7-dihydro-8-iodo- (9CI) (CA INDEX NAME)



RN 56046-36-7 HCAPLUS
CN 6H-Purin-6-one, 8-bromo-1,7-dihydro- (9CI) (CA INDEX NAME)



RN 64761-27-9 HCAPLUS
CN 1H-Purine-2,6-dione, 3,7-dihydro-8-iodo- (9CI) (CA INDEX NAME)



L9 ANSWER 14 OF 16 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1995:544412 HCAPLUS
DOCUMENT NUMBER: 123:251
TITLE: Enhancement of **immunostimulatory** activity by dual substitution of C8-substituted guanine ribonucleosides: correlation with increased cytokine secretion
AUTHOR(S): Pope, Barbara L.; Chourmouzis, Erika; Lee, Spencer; Goodman, Michael G.
CORPORATE SOURCE: R. W. Johnson Pharmaceutical Research Institute, Don Mills, ON, Can.
SOURCE: Journal of Immunotherapy with Emphasis on Tumor Immunology (1995), 17(2), 98-108
CODEN: JIEIEZ; ISSN: 1067-5582
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Guanine ribonucleosides with single substitutions at the C8 position (monosubstituted) or with dual substitutions at the C8 and N7 positions (disubstituted) up-regulate a spectrum of immunol. responses, including cytolytic responses to tumor cells. The current studies were undertaken to det. the effects of dual substitution on a no. of nucleoside-inducible immunol. parameters. To do so, two monosubstituted analogs, 8-bromoguanosine and 8-mercaptoguanosine, were directly compared with two disubstituted analogs, 7-methyl-8-oxoguanosine and 7-allyl-8-oxoguanosine (loxoribine). All of the compds. enhance natural killer (NK) activity, lymphocyte proliferation, and antibody prodn. in dose-dependent fashion. However, the potency and maximal activity of the disubstituted analogs are considerably greater than those of the monosubstituted analogs. Spleen cells stimulated for 48 h with the disubstituted compds. produce immunoreactive interleukin (IL) 1.alpha., IL-6, tumor necrosis factor-.alpha. (TNF.alpha.); and interferon-.gamma. (IFN.gamma.). Monosubstituted analogs induce lower quantities of IL-6, TNF.alpha., and IFN.gamma. and fail to induce detectable levels of IL-1.alpha.. Total IFN activity, assessed by viral inhibition assay, is also lower for the monosubstituted analogs. Augmentation of antibody secretion by B cells is diminished for neither mono- nor disubstituted compds. upon incubation

with anti-cytokine antibodies. In contrast, anti-IFN.alpha..beta. markedly reduces the effects of monosubstituted analogs on NK activity but has less marked effects on NK induction by the disubstituted compds. A similar pattern of differences is seen for lymphocyte proliferation. Thus, although the analogs induce synthesis of several cytokines, to date only IFN.alpha..beta. appears directly involved in enhancement of NK activity and lymphocyte proliferation. The present data do not, however, exclude the existence of an autocrine stimulatory mechanism not susceptible to inhibition by anti-cytokine antibodies.

CC 1-3 (Pharmacology)

ST **immunostimulant** guanine ribonucleoside cytokine secretion

IT **Immunostimulants**
(enhancement of **immunostimulatory** activity by dual substitution of C8-substituted guanine ribonucleosides in relation to increased cytokine secretion)

IT Lymphocyte
(proliferation; enhancement of **immunostimulatory** activity by dual substitution of C8-substituted guanine ribonucleosides in relation to increased cytokine secretion)

IT Molecular structure-biological activity relationship
(**immunostimulating**, enhancement of **immunostimulatory** activity by dual substitution of C8-substituted guanine ribonucleosides in relation to increased cytokine secretion)

IT Lymphokines and Cytokines
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(interleukin 1.alpha., enhancement of **immunostimulatory** activity by dual substitution of C8-substituted guanine ribonucleosides in relation to increased cytokine secretion)

IT Lymphokines and Cytokines
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(interleukin 6, enhancement of **immunostimulatory** activity by dual substitution of C8-substituted guanine ribonucleosides in relation to increased cytokine secretion)

IT Lymphocyte
(natural killer cell, enhancement of **immunostimulatory** activity by dual substitution of C8-substituted guanine ribonucleosides in relation to increased cytokine secretion)

IT Lymphokines and Cytokines
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(tumor necrosis factor-.alpha., enhancement of **immunostimulatory** activity by dual substitution of C8-substituted guanine ribonucleosides in relation to increased cytokine secretion)

IT Interferons
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(.alpha./.beta., enhancement of **immunostimulatory** activity by dual substitution of C8-substituted guanine ribonucleosides in relation to increased cytokine secretion)

IT Interferons
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(.gamma., enhancement of **immunostimulatory** activity by dual substitution of C8-substituted guanine ribonucleosides in relation to increased cytokine secretion)

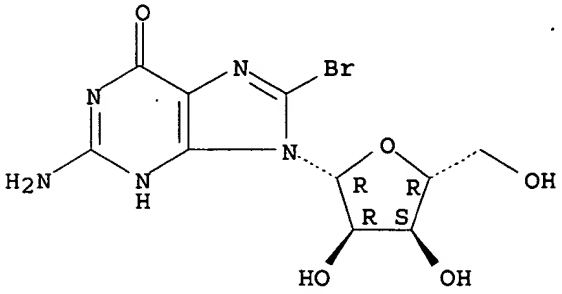
IT **4016-63-1**, 8-Bromoguanosine 26001-38-7, 8-Mercaptoguanosine 28007-87-6, 7-Methyl-8-oxoguanosine 121288-39-9, Loxoribine

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(enhancement of **immunostimulatory** activity by dual substitution of C8-substituted guanine ribonucleosides in relation to increased cytokine secretion)

IT **4016-63-1**, 8-Bromoguanosine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(enhancement of **immunostimulatory** activity by dual substitution of C8-substituted guanine ribonucleosides in relation to increased cytokine secretion)

RN 4016-63-1 HCAPLUS
CN Guanosine, 8-bromo- (7CI, 8CI, 9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L9 ANSWER 15 OF 16 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1994:692072 HCAPLUS
DOCUMENT NUMBER: 121:292072
TITLE: Antiviral and **immunomodulating** inhibitors of experimentally-induced Punta Toro virus infections
AUTHOR(S): Sidwell, Robert W.; Huffman, John H.; Barnard, Dale L.; Smee, Donald F.; Warren, Reed P.; Chirigos, Michael A.; Kende, Meir; Huggins, John
CORPORATE SOURCE: Institute for Antiviral Research, Utah State University, Logan, UT, 84322-5600, USA
SOURCE: Antiviral Research (1994), 25(2), 105-22
CODEN: ARSRDR; ISSN: 0166-3542
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A major component of a US Army Medical Research and Development Command-supported program to discover and develop new drugs for the treatment of Rift Valley fever, sandfly fever, and Crimean-Congo hemorrhagic fever has been to study candidate test materials against hepatotropic infections of C57BL/6 mice induced by the related but less biohazardous Punta Toro virus (PTV). The effects of 75 compds., some of which were considered immunomodulators in their primary mechanism of activity, were studied in the PTV infection model. Of these, ribavirin, ribamidine, ribavirin 2',3',5'-triacetate, tiazofurin, tiazofurin-5'-monophosphate, tiazofurin-2',3',5'-triacetate, selenazofurin, pyrazofurin, 3-deazaguanine, and 3-deazaguanosine were considered significantly inhibitory, acting against the infection by a direct antiviral (non-immunomodulatory) fashion. These compds. had

therapeutic indexes (TI) ranging from .gtoreq.5 to 65, using increased survivors as the evaluation parameter. Immunomodulators considered significantly inhibitory to this infection were poly (ICLC), ampligen, human recombinant interferon-.alpha.-A/D, MVE-1, MVE-2, AM-3, AM-5, mannozym, bropirimine, CL246,738, phenyleneamine, and 7-thia-8-oxoguanosine. Utilizing increased survivor nos. as measure of activity, these inhibitors had TI ranging from .gtoreq.16 to 1000. Other antiviral effects exerted by the active compds. included redn. of hepatic icterus, lowered serum glutamic oxaloacetic and pyruvic acid transaminases, and inhibition of recoverable serum and liver virus titers. The active immunomodulators were significantly effective when therapy was initiated as late as 48 h after virus inoculation, at a time when clin. signs of the PTV disease were being manifested in the animal.

CC 1-5 (Pharmacology)

ST Punto Toro virus virucide **immunomodulator**

IT **Immunomodulators**
Virucides and Virustats
(antiviral and **immunomodulating** inhibitors of exptl.-induced Punta Toro virus infections)

IT Polysaccharides, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(glucomannon; antiviral and **immunomodulating** inhibitors of exptl.-induced Punta Toro virus infections)

IT Virus, animal
(Punta Toro, antiviral and **immunomodulating** inhibitors of exptl.-induced Punta Toro virus infections)

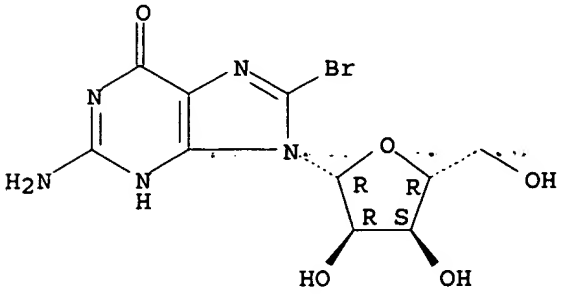
IT Interferons
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(.alpha., A/D; antiviral and **immunomodulating** inhibitors of exptl.-induced Punta Toro virus infections)

IT 54-25-1, 6-Azauridine 62-53-3, Benzenamine, biological studies 66-81-9, Actidione 145-63-1, Suramin 471-53-4, Glycyrrhetic acid 734-22-5, CL 259763 3930-19-6, Streptonigrin **4016-63-1**, 8-Bromoguanosine 6742-12-7, Formycin 12758-40-6, GE132 17073-78-8 19622-83-4, 7-Deoxynarciclasine 25451-90-5 27089-56-1 27100-68-1, MVE-1 29477-83-6, Narciclasine 29725-42-6 30868-30-5, Pyrazofurin 36703-88-5, Isoprinosine 36791-04-5, Ribavirin 38640-92-5, Ampligen 41729-52-6, 3-Deazaguanine 42400-25-9 56039-11-3, 3-Deazaguanosine 56741-95-8, Bropirimine 58151-87-4 59643-91-3, Imexon 59789-29-6, Poly(ICLC) 60084-10-8, Tiazofurin 61367-58-6 63166-73-4, Phyllanthoside 68652-43-7, Mannozym 72161-05-8, Ribavirin 2',3',5'-triacetate 72301-79-2, Enviroxime 81541-26-6, CL 246738 82372-67-6, Pseudolycorine hydrochloride 83161-83-5, Tiazofurin-5'-monophosphate 83705-13-9, Selenazofurin 87139-86-4, AM 3 87745-28-6, Bryostatin 2 96203-70-2, Pancratistatin 99258-56-7, Oxamisole 104942-51-0 119567-79-2, Ribamidine 122970-40-5, 7-Thia-8-oxoguanosine 141776-53-6 150316-23-7, Neurotropin 159192-47-9 159192-48-0 159192-49-1
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(antiviral and **immunomodulating** inhibitors of exptl.-induced Punta Toro virus infections)

IT **4016-63-1**, 8-Bromoguanosine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological

study); USES (Uses)
(antiviral and **immunomodulating** inhibitors of exptl.-induced Punta Toro virus infections)
RN 4016-63-1 HCAPLUS
CN Guanosine, 8-bromo- (7CI, 8CI, 9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L9 ANSWER 16 OF 16 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1992:91376 HCAPLUS
DOCUMENT NUMBER: 116:91376
TITLE: Therapeutic nucleosides
INVENTOR(S): Koszalka, George Walter; Burns, Charlene Louise; Krenitsky, Thomas Anthony; Rideout, Janet Litster
PATENT ASSIGNEE(S): Wellcome Foundation Ltd., UK
SOURCE: Eur. Pat. Appl., 35 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 421819	A1	19910410	EP 1990-310965	19901005
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
US 5068320	A	19911126	US 1989-417989	19891006
CA 2027052	AA	19910407	CA 1990-2027052	19901005
AU 9063863	A1	19910411	AU 1990-63863	19901005
AU 637831	B2	19930610		
HU 55028	A2	19910429	HU 1990-6358	19901005
JP 03188022	A2	19910816	JP 1990-268245	19901005
US 5185437	A	19930209	US 1991-753060	19910831

PRIORITY APPLN. INFO.: US 1989-417989 19891006
GB 1987-8512 19870409
GB 1987-12691 19870529
GB 1987-23013 19870930
US 1988-179435 19880408
OTHER SOURCE(S): MARPAT 116:91376
AB 6-Substituted 2',3'-dideoxynucleosides [I; R1, R3 = H, amino; R2 = halo, heterocyclyl, imidazolylthio, amino, C1-6 alkoxy (un)substituted with C3-6 cycloalkyl, C3-8 cycloalkyloxy, aryloxy, aralkyl, etc.] for use in the treatment or prophylaxis of hepatitis B virus (HBV) infections are prepd. A specific novel compd., 6-(cyclopropylmethylamino)purine-9-.beta.-D-2',3'-dideoxyribofuranoside, was prepd. by reacting 6-cyclopropylmethylaminopurine with 3'-deoxythymidine in DMF/DMSO for use in

the treatment or prophylaxis of HBV and human retrovirus (e.g. human immunodeficiency virus) infections, and pharmaceutical formulations contg. I were given.

IC ICM C07D405-04
ICS A61K031-70

CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 28

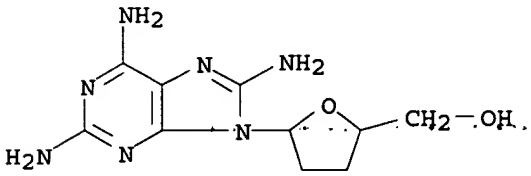
IT Virus, animal
(human **immunodeficiency** 1, infection with, prophylaxis and treatment of, with purine deoxyribofuranoside derivs.)

IT 85326-07-4P 118191-23-4P 120503-28-8P 120503-29-9P 120503-30-2P
120503-31-3P 120503-32-4P 120503-33-5P 120503-34-6P 120503-35-7P
120503-36-8P 120503-37-9P 120503-38-0P 120503-40-4P 120503-41-5P
120503-42-6P 120503-43-7P 120503-44-8P 120503-45-9P 120503-46-0P
120503-47-1P 120503-48-2P 120503-49-3P 120503-50-6P 120503-51-7P
120503-52-8P 120503-53-9P 120503-54-0P 120503-55-1P 120503-56-2P
120503-57-3P 120503-58-4P **120503-59-5P** 120503-60-8P
120503-61-9P 120503-62-0P 120503-63-1P 120503-64-2P 120503-65-3P
135867-83-3P 135867-84-4P 135867-85-5P
RL: **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of, as virucide)

IT **120503-59-5P**
RL: **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of, as virucide)

RN 120503-59-5 HCAPLUS

CN Adenosine, 2,8-diamino-2',3'-dideoxy- (9CI) (CA INDEX NAME)



Structure search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                ACT YOUNG2/A
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L3              STR
L4         5452 SEA FILE=REGISTRY SSS FUL L3
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L6          2896 S L4
L7           217 S L6 (L) THU/RL
L8            17 S IMMU? AND L7
L9            16 S L8 NOT L5
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USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
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Property values tagged with IC are from the ZIC/VINITI data file
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STRUCTURE FILE UPDATES:     3 NOV 2002  HIGHEST RN 469858-87-5
DICTIONARY FILE UPDATES:    3 NOV 2002  HIGHEST RN 469858-87-5

TSCA INFORMATION NOW CURRENT THROUGH MAY 20, 2002

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available.  See HELP
PROPERTIES for more information.  See STNote 27, Searching Properties
in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf
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claims 5 includes structures/compounds in claim 19

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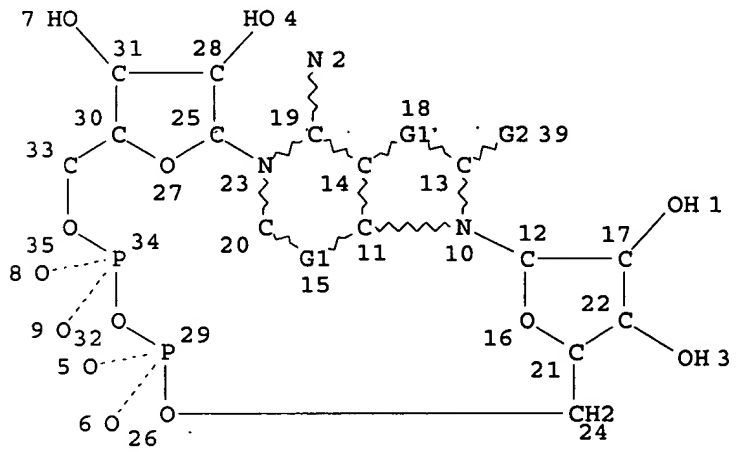


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DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RSPEC I
NUMBER OF NODES IS  39

STEREO ATTRIBUTES: NONE
L2             7 SEA FILE=REGISTRY SSS FUL L1
```
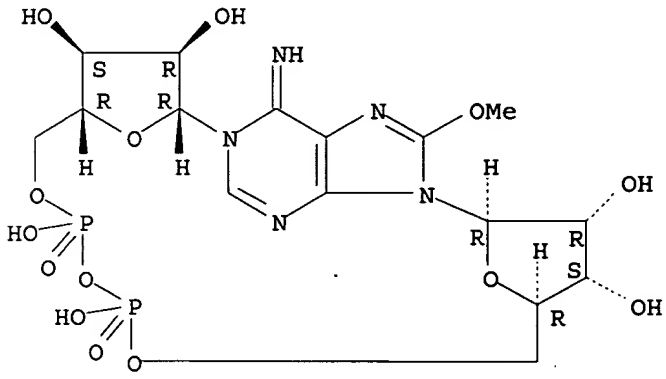

100.0% PROCESSED 36 ITERATIONS 7 ANSWERS
SEARCH TIME: 00.00.02

=> d l2 ide can 1-7

L2 ANSWER 1 OF 7 REGISTRY COPYRIGHT 2002 ACS
RN 398460-86-1 REGISTRY
CN Adenosine 5'-(trihydrogen diphosphate), 8-methoxy-1-.beta.-D-ribofuranosyl-, intramol. P',5''-ester (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C16 H23 N5 O14 P2
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER

Absolute stereochemistry.



1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

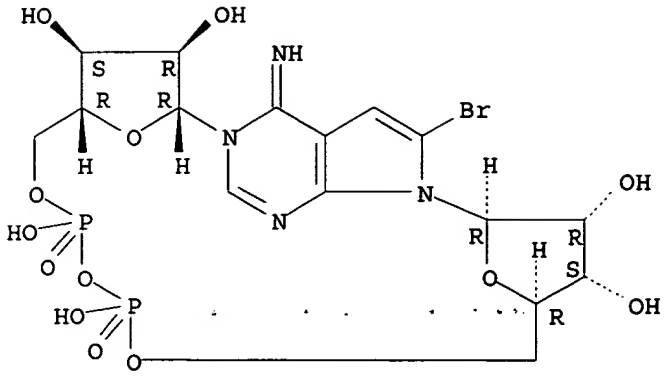
REFERENCE 1: 136:177974

L2 ANSWER 2 OF 7 REGISTRY COPYRIGHT 2002 ACS
RN 213894-69-0 REGISTRY
CN 4H-Pyrrolo[2,3-d]pyrimidin-4-imine, 6-bromo-3,7-dihydro-3-[5-O-[hydroxy(phosphonooxy)phosphinyl]-.beta.-D-ribofuranosyl]-7-.beta.-D-ribofuranosyl-, intramol. P'.fwdarw.5'-ester, compd. with N,N-diethylethanamine (1:1) (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C16 H21 Br N4 O13 P2 . C6 H15 N
SR CA
LC STN Files: CA, CAPLUS

CM 1

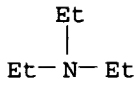
CRN 189876-06-0
CMF C16 H21 Br N4 O13 P2

Absolute stereochemistry.



CM 2

CRN 121-44-8
CMF C6 H15 N



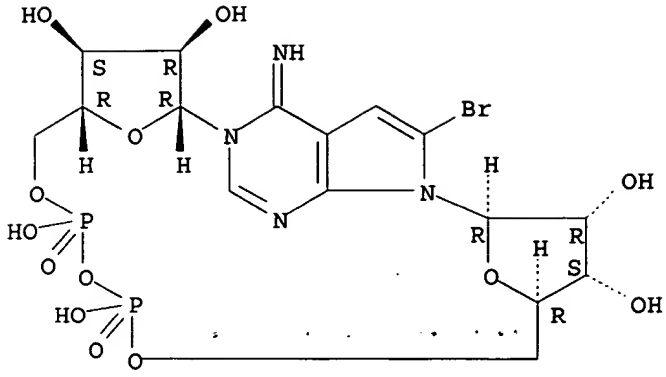
1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 129:276237

L2 ANSWER 3 OF 7 REGISTRY COPYRIGHT 2002 ACS
RN 189876-06-0 REGISTRY
CN 4H-Pyrrolo[2,3-d]pyrimidin-4-imine, 6-bromo-3,7-dihydro-3,7-di-.beta.-D-ribofuranosyl-, cyclic P.fwdarw.5':P'.fwdarw.5''-(dihydrogen diphosphate) (9CI) (CA INDEX NAME)
FS STEREOSEARCH
DR 213894-68-9
MF C16 H21 Br N4 O13 P2
CI COM
SR CA
LC STN Files: CA, CAPLUS


claim 19

Absolute stereochemistry.



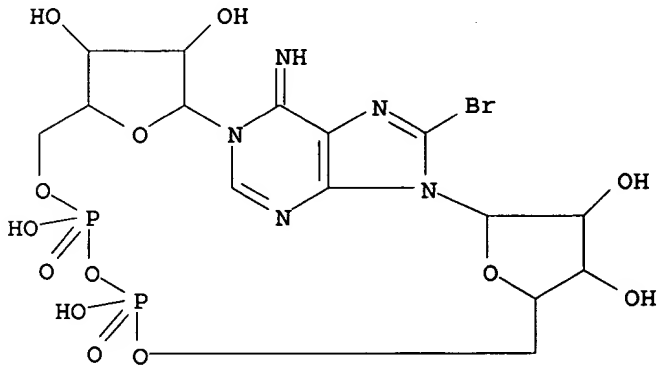
3 REFERENCES IN FILE CA (1962 TO DATE)
3 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 130:350258

REFERENCE 2: 127:147585

REFERENCE 3: 126:343786

L2 ANSWER 4 OF 7 REGISTRY COPYRIGHT 2002 ACS
RN 151898-26-9 REGISTRY
CN Adenosine 5'-(trihydrogen diphosphate), 8-bromo-1-.beta.-D-ribofuranosyl-, intramol. P'.fwdarw.5''-ester (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 8-Bromo-cADPR
MF C15 H20 Br N5 O13 P2
SR CA
LC STN Files: BIOSIS, CA, CAPLUS, CHEMCATS, CSCHEM, TOXCENTER, USPATFULL



claim 19

3 REFERENCES IN FILE CA (1962 TO DATE)
3 REFERENCES IN FILE CAPLUS (1962 TO DATE)

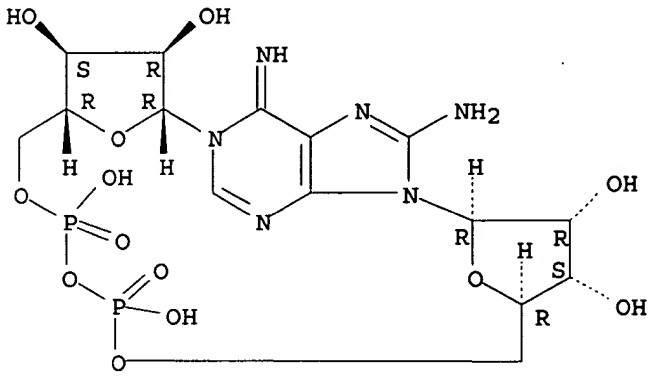
REFERENCE 1: 131:197977

REFERENCE 2: 124:317786

REFERENCE 3: 120:28268

L2 ANSWER 5 OF 7 REGISTRY COPYRIGHT 2002 ACS
RN 151898-25-8 REGISTRY
CN Adenosine 5'-(trihydrogen diphosphate), 8-amino-1-.beta.-D-ribofuranosyl-, intramol. P'.fwdarw.5''-ester (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 8-Amino-cADPR
FS STEREOSEARCH
DR 170869-45-1
MF C15 H22 N6 O13 P2
SR CA
LC STN Files: BIOSIS, CA, CAPLUS, CHEMCATS, MEDLINE, TOXCENTER, USPATFULL

Absolute stereochemistry.



6 REFERENCES IN FILE CA (1962 TO DATE)
6 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 134:191049

REFERENCE 2: 131:197977

REFERENCE 3: 130:139585

REFERENCE 4: 125:191842

REFERENCE 5: 124:317786

REFERENCE 6: 120:28268

L2 ANSWER 6 OF 7 REGISTRY COPYRIGHT 2002 ACS
RN 150424-94-5 REGISTRY
CN Adenosine 5'-(trihydrogen diphosphate), 8-azido-1-.beta.-D-ribofuranosyl-, intramol. P'.fwdarw.5''-ester (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 8-Azido-cADPR
MF C15 H20 N8 O13 P2
SR CA
LC STN Files: CA, CAPLUS, CHEMCATS, MEDLINE, USPATFULL